THE ANIMAL ALKALOIDS

AND AUTO-INTOXICATION

IN HEALTH AND DISEASE.

A. M. BROWN, M. D.

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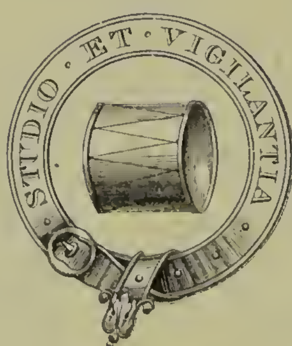

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The Animal Alkaloids

AND

AUTO-INTOXICATION IN HEALTH AND DISEASE.

THE

ANIMAL ALKALOIDS,

CADAVERIC AND VITAL;

OR,

THE PTOMAINES AND LEUCOMAINES

CHEMICALLY, PHYSIOLOGICALLY AND PATHOLOGICALLY CONSIDERED IN RELATION TO SCIENTIFIC MEDICINE.

BY A. M. BROWN, M.D.

With an Introduction by

PROFESSOR ARMAND GAUTIER,

Of the Faculté de Médecine of Paris, and Member of the Académie de Médecine, and of the Académie des Sciences.

SECOND EDITION.

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PREFACE TO THE SECOND EDITION.

THE author, in proposing to himself the issue of a second and enlarged edition of his Treatise on the Animal Alkaloids, believes that in so doing he will supply a professional want. The original work is now out of print, though only put through the press within the last eighteen months. Its so rapid exhaustion he naturally attributes to the high and intrinsic interest attaching to the subject to which this work has directed attention.

The startling problems involved in the study of the Animal Alkaloids is no longer exclusively limited to the special department of the experimental chemist and physiologist; laying claim as it does to a much wider range, it should now be made accessible to the student of medicine generally. The present work in its revised and enlarged form the author thinks well calculated to meet this requirement and purpose.

Strictly practical in arrangement, the work divides itself into five parts, the first of which deals with the

ptomaines or cadaveric alkaloids. The second treats of the leucomaines, or vital alkaloids, each class being investigated under its various aspects, whether chemical, toxic, or medico-legal. The third part indicates the physiological origin of the leucomaines and their *rôle* in auto-intoxication in disease. The fourth and fifth parts, in which is traced out the farther developments of the subject, is devoted to material entirely new, which has been brought down to the latest date.

Though not proposing to be a treatise that shall be thoroughly exhaustive, it will admittedly be found to supply what has hitherto not existed in print, namely, an adequate introduction to the subject in all its bearings.

The accompanying table of contents will be found to exhibit with sufficient clearness the character and objects of the present publication.

A. M. B.

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PREFACE TO THE FIRST EDITION.

In my essay on the Origin of Contagia, considered from the evolutional point of view, two editions of which were published in 1884, the genesis and transformation of morbific elements, organic and inorganic, were reviewed; the physiological alkaloids as factors in etiology and general pathology were noted, and their action as auto-infectants, or as toxic agents in poisoning from inoculation of putrid animal matter prophylactically or otherwise, indicated.

The startling problems the study of the alkaloids envolve, having hardly been submitted to the scientific student here in England, I concluded by expressing my intention of entering more fully and more closely into the subject in a future work. The series of papers on the animal alkaloids—a list of which is here appended—which from time to time have been published by me since, were an earnest that the design was being carried out. The present treatise which I have now the pleasure of submitting for the

consideration of the competent is the fulfilment of my promise.

Without the encouragement and aid of Continental workers in this department, the task would have been impossible; it is, consequently, with no small pleasure I have to acknowledge my great indebtedness, in the first place, to Professor Armand Gautier, whose name occupies the chief position in connection with the subject, and who has done me the honour of contributing the lucid introduction to the treatise. Secondly, to Professor Michel Peter, who has done so much to advance the claims of the animal alkaloidal factor in pathology and clinical medicine; and, thirdly, to Professor Hugounenq, author of an excellent *résumé*, and whose valuable bibliography, supplemented by myself to the present date, finds a suitable place in the appendix, and which will doubtless be estimated at its proper worth by all who are engaged or take an interest in this special department of research. From these generous sources I have been enabled not only to avail myself of what has been hitherto recorded, but also of research material still unpublished, and to note current investigations that promise farther enrichment of this new departure in science. Evidence of this will be seen in Bouchard's "Lessons on Auto-intoxication in Disease," and Sir

William Aitken's Netley lecture, "On the Animal Alkaloids in their Pathological Relations," both now in course of publication, and which will shortly be available.

In a department of science so new and novel, many points of controversial character necessarily present themselves. I may be permitted to say that I have neither courted nor avoided them. As regards my own particular views, I trust that they are evident, but not obtrusive.

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INTRODUCTORY.

Introduction

BY

PROFESSOR ARMAND GAUTIER.

INTRODUCTION.

THE essential phenomena of cellular life, vegetal or animal, are still too little known in their mechanism, and [illegible] in their effects, to permit of our determining the intimate causes of their evolution, normal or abnormal, on which health and disease depend. What may, however, be positively affirmed is, that these phenomena are entirely physico-chemical in their nature, and that if the reason of their succession still escapes detection they are necessarily subject to the general law which requires that force in all its forms—heat, muscular activity, chemical or nervous action, &c.—is the result of a transformation of mechanical energy, potential or actual, present in the material substance of each cell.

It is now well known that in the case of living things, as in that of inert substances, the modifications which render force appreciable and utilisable, are of two kinds. In the case of the first, it results from molecular modifications

brought about in matter without the intervention of oxygen. Organisms which derive their force vitality entirely from this interior source, are those which M. Pasteur has named *anaerobic* and belong to the lower order of ferments. But I have shown elsewhere that, contrary to what was *a priori* supposed, the life of the larger animals is in a great measure—nearly one-fifth—also *anaerobic.* The second source of vital force results from the chemical combination of substances, and particularly in the case of those which are combustible, in their union with oxygen. Those organisms which more especially derive their force from internal combustions are *aerobic.* Some of them are vegetable, but in general they belong to the animal kingdom. They absorb oxygen, burn the material substance of their cells, incessantly give off carbonic acid, water, urea, &c., correlatively benefiting by the force resulting from these combustions.

In both cases the vital products become unsuitable for the maintenance of the vital functions of the cell which formed them ; they must be got rid of. The animal would very soon succumb were the carbonic acid, urea, water, and even the heat, which it incessantly produces, to accumulate within its organism. But

in the case of *anaerobic* life, the products that arise and form without the intervention of oxygen, and more particularly those which result from the splitting up or disintegration of albumenoid material, are especially dangerous. They are of the nature of those substances which result from all putrid bacterial fermentations. In the first part of the present work it will be seen, that bacterial *anaerobic* life gives rise to certain alkaloids, besides other very poisonous bodies, which are also to be met with in cadaveric matters, and which, by reason of this, have received the name of ptomaines. Those of this class which are constantly present in prolonged putrefactive fermentations, belong to the pyridic and hydropyridic series; they do not differ widely from the poisonous bases of hemlock and tobacco. It is only recently that there has been detected in the products of the newer fermentations, the presence of alkaloid substances more powerful still. Such, for instance, is muscarine, the poisonous principle of certain species of the mushrooms. If, then, I have shown that we live in part *anaerobically*, alkaloids analogous in nature ought to form in the animal organism. This experiment has confirmed, and I have given to these bases the name of *leucomaines*, a term which is merely meant to indicate their albumenoid origin.

The products of life, aerobic or anaerobic, cannot be retained within the organism for any length of time with impunity; normally they undergo destruction and excretion by economic processes, which are constantly in operation. But if from any cause the functional play is interrupted; should there be emotional disturbance of the nervous centres; should sudden chills suppress the action of the skin, or insufficient aeration of the blood take place; or, finally, if from any less obvious cause, leucomain products are more abundantly formed within the cells, or be so defectively absorbed, excreted, or oxydized as that the blood becomes charged with them, they are carried to the nervous centres which regulate the central life and function as a whole; immediately disorder becomes general, complete, and necessarily assumes progressive forms—in a word, disease declares itself and undergoes development.

This admitted, facts must not, however, be too exclusively regarded. We must not too hastily assume that the succession of morbid phenomena are thus to be explained in every case. Without doubt, many pathological conditions arise from disarrangement of nutrition, assimilation, disassimilation, secretion and hæmatose—are, in a word, veritable auto-infec-

tions. Still, there are cases in which we cannot possibly ignore the presence of causes, which the organism would seem incapable of exciting spontaneously. We do not, for instance, observe syphilis, measles, variola, anthrax, nor the generality of maladies known as contagious and specific—with possibly the exception of army-typhus—appear spontaneously, even in those unhealthily predisposed, without previous contact or relation, direct or indirect, with infected subjects. To M. Pasteur is due the merit of having demonstrated that in the majority of such cases, we can obtain from the disease subject a microbe, specific, cultivable and capable of reproducing itself apart from the animal organism, and which, when introduced into a healthy organism, gives rise to the primitive or original malady. But who does not see that these important facts are phenomenally characteristic of the life of the cells, as they normally comport themselves in the higher animal organisms? A ferment or specific *microbe* lives after the fashion of one of our tissue cells now *aerobically*, as is the case in anthrax; again, *anaerobically*, as when septicemia is taken as an example. It cannot escape that law which requires that every cell that lives produces detritus—extractive matter, ptomaines,

leucomaines—which are the proximate causes of its powerful action on the organism. But in this new case, the foreign cells comport themselves much in the mode that cancer cells, for example, do, exhibiting a life, a power of prolificity so active as to rapidily invade the whole economy with the dangerous products of their evolution.

It would, then, be erroneous to insist, with the over-fervent followers of their master, that all maladies result from the evolution of a specific microbe in the organism. There are causes of disease which are resident within ourselves, that remain inoffensive whilst elimination and oxydation of detritus is normally operative, that give rise to disease if from some cause or other the detritus accumulates in the economy and acts upon the nervous centres. But to those morbific agents, which our living tissues incessantly dispose of, must be added the operation, though in rarer instances, of those derivable from the normal life of those parasitic cells which have been named *microbes* or ferments, and which are found to accompany the generality of contagious or virulent diseases.

The ptomaines and leucomaines, like the extractive matters, urea, urides, carbonic acid, the oxalates and ammoniacal salts, are the vital re-

liquæ or residue material, effete and pernicious, which may become the cause of disease, no matter how they originate, that is, arise in the normal cells of the organism from within, or in the microbic cell from without. Of all the extractive composite residua the alkaloids of animal origin, which the present work treats of, are worthy of the deepest interest. It is only now that they have become familiar to us. They claim our special study from the fact of their constant presence in normal secretions, and must be classed with the most active agents known. I am consequently of opinion that the excellent work by Dr. A. M. Brown will have a very special interest for competent enquirers; that it will give a stimulus to investigations, new and fruitful in elucidation of a question the most essentially humane—the cause and the mechanism of life, health, and disease.

ARMAND GAUTIER.

PARIS, *July* 14, 1887.

The Cadaveric Alkaloids or Ptomaines.

PART I.

The detection of animal organic bases, even those of putrefactive origin, it must be admitted, is not a recent fact in modern science. So very little importance was, however, attached to the few carelessly observed alkaline matters, that until 1872, every toxic alkaloid substance detected in the course of medico-legal investigations by experts, was regarded as having been introduced into the system during life. Theoretic preconception sufficiently accounts for this ; scientific conservativism is as difficult to overcome as any other form. In the beginning of the century, the power of plants to form alkaloids had been conceded : for more than half a century later the like privilege was dogmatically refused to animal organisms, in entire ignorance of the fact that the efficient agents of fermentation were but the simplest forms of vegetable existence,—in fact, the connecting link between the plant and animal.

It is true that the proof with which gratuitous hypotheses could be confronted was both obscure and incomplete. In 1822, Gaspard and Stick to begin with, had detected a venomous principle in cadaverous extracts. Panum in 1856, taking up the subject, found that putrid matters contained a poison of great activity which was neither albumenoid nor alkaloid. In consequence of the interest excited by the investigations of the latter, which promised to throw light upon the causes of putrid infection, several of the German schools instituted a comparative study of its etiological action. Between 1856 and 1868, various memoirs appeared, of which those of Hemmer, Schwerminger, Muller, Schmitz, Weidenbáum, though important, did little more than confirm the work of Panum.

In 1868, Bergmann and also Schmiedeberg obtained from the extracts of putrid beer a nitrogenous crystallizable substance which they called sepsine. Its subsequent presumed discovery in septicemic blood dependent on purulent absorption, the pathological speculations which it gave rise to, associating with them the names of Dupré and Bence Jones, is now a matter of medical history, and need not be here disturbed — septicemia and purulent in-

fection have passed through speculative phases since, equally interesting, and quite as time-serving. Following on the illusory sepsine acquisition, Zuelzer and Sonnenschein made known the fact of their obtaining from putrid meat a venomous nitrogenous body, which induced dilatation of the pupil, a property permitting them to compare it with atropine.

When Selmi and Gautier entered on their work, this included almost all that had been done ; namely, observations for the most part disconnected, ill-defined or questionable, of substances—Panum's putrid poison excepted — whose genesis, nature, and chemical composition were but names and notions. As regards those alkaline products normally present in the animal economy during life, it is also well to note that though positively, if not theoretically, a greater advance had been attained. But, in their turn the vital alkaloids, as will be seen when they come to be treated of, were not less subject to misconception and suspicion.

Such was the state of the enquiry when about 1870 M. Gautier, in the course of researches on the albumenoids under various conditions, observed that those substances when left to putrefy became strongly ammoniacal. He observed that on distilling normal urines which, in gen-

eral, are acid, there passed into the recipient an alkaline liquid, containing trimethylamine. This fact confirmed led to the suspicion, that the alkalinity of putrid liquids was not entirely due to the presence of ammonia; closer investigation showed that such was the case. Later on, in the course of 1872, he ascertained the fact that fibrine of the blood, when left to liquefy in water during the summer months, furnished, besides the products then known, a small quantity of various complex alkaloid substances fixed or volatile. His subsequent researches on the bacterial destruction of the albumenoids gave fullest confirmation of these facts.

While in France Gautier as a chemico-physiologist pursued his researches, in Italy Selmi, as a medico-legal expert, was similarly engaged. With different objects and from different aspects both dealt with the problem, independently of each other, both were experimentally and logically working out the same result. The Italian toxicologist, in examining the dead body of a subject supposed to have been poisoned, detected an alkaloid which he was unable to identify with any body then known as such. A second instance, leading to a similar result, led him to suspect that the presence of the alkaloid

might be owing to physio-chemical action after death rather than to accidents during life.

Early in 1872, Selmi communicated to the Academy of Science of Bologna, a lengthy memoir, embodying his conclusions :—I. That the stomach of persons who had died from natural causes, contained substances which comport themselves in the presence of reagents precisely as the vegeto-alkaloids do. II. That these products are neither kreatine nor kreatinine, nor tyrosine. III. That similar substances are present in alcohol, in which anatomical specimens have been preserved. Amongst toxicologists these views were received with some surprise, but the celebrated expert, by carefully carrying on researches on exhumed bodies, proved to demonstration that veritable organic toxic alkaloids, analogous to those of vegetable origin, were a constant accompaniment of the process of putrefactive decomposition.

The objections raised, to be repeated later on in the inquiry, were numerous. Might not the presence of the substances be accounted for by vegetable ingesta, or medicine taken during life. And as no analysis had been made, it was suggested that they might be some pseudo-alkaloid or another, such as kreatine or kreatinine, amides rather than alkalies, &c. ; in fact,

errors of the professor himself, owing to defective mothods of investigation, left room for doubt.

Replying to these objections, Selmi, in 1877, conclusively announced that by subjecting pure albumen to putrefaction, free from atmospheric contact, he had been enabled to separate two new alkaloids.

It would appear then that it was in 1876 that Selmi satisfied himself that albumenoid material undergoing putrefaction is the origin of those cadaveric alkaloids which he had met with in earlier operations. But this result, as we have seen, had already been attained in 1873, by Armand Gautier, and by a method that was precise and clear beyond dispute ; fibrine washed and free of all extractive matters, yielded alkaloids in crystallizable salts, strictly derived from albumenoid matters, these substances being alone employed in his experiments.

It is well to be reminded of these facts, for here an honour seems to have been somewhat misawarded. While fully recognizing the claims of Selmi, and the remarkable extension his researches have given to this subject, it is incontestable that M. Gautier was the first to make known the fact that it is really the proteid substances which supply the new class of alkaloids

which he and Selmi had independently discovered. This, however, Selmi himself amply acknowledged. The circumstance is alluded to with no view of disputing the importance of his work. His researches on the alkaloids, which he succeeded in extracting from cadaveric products and which he first observed showed none of the reactions of then known alkaloids, is sufficient proof of his scientific sagacity. If Selmi failed to explain the formation of the new bodies he was, none the less, quick to seize their origin, and the importance of their discovery. His name must therefore justly be regarded as first in modern toxicology.

I.

Putrefactive Origin and Genesis.

The discovery of the cadaveric alkaloids known as the ptomaines being fully treated, their origin has now to be considered. These alkaloids being the product of putrefaction, their origin must be sought for in the bacterial destruction of animal tissues, which forms the necessary introduction to their special study. Keeping this fact in view, we now proceed to sift the putrefactive process of nitrogenous organic substances, not precisely as a whole, but with reference rather to the elaboration of the alkaloid albumenoid derivatives.

Detected in the animal economy after death, the experimental extraction of the alkaline basic residue is affected by operating on the dead body of man or the carcases of animals. For the investigator this difference of source is immaterial. The nature and object of investigation is the same in either case ; from first to last phenomenally the destructive process being

identical, they have the same significance and must be so noted. When vitality ceases and the lifeless body is abandoned to decay, it is observed that putrefactive indications for a time are neither well defined nor simultaneous. Loss of heat, rigidity and discoloration of the subject, follow in succession, and, as with the carcase fragments, if not so markedly, soon acquire an acid odour accompanied with copious clear albumenous exudation, carbonic acid and hydrogen gases are disengaged, and during the first stage, without a trace of nitrogen. The mass medium exhibits a progressive *rôle* of fermentation, at first lactic, then butyric, and looks as if it had been sweetened. Towards the fifth or sixth day in the carcase fragments, the albumenoid material, which till now remained inactive, in its turn ferments; the disengagement of nitrogen, sulphuretted and phosphoretted hydrogen mingled with carbonic acid, now takes place; the medium soon becomes alkaline; ammonia is set free giving the finishing characteristic of the putrefactive condition, as it is ordinarily conceived to be.

When fish-flesh is substituted for animal tissues, the sequence of phenomena is somewhat different. In the latter, lacto-butyric fermentation due to a preliminary absence of the

hydrates of carbon, which, in the living animal tissues, are seemingly in union with the albumenoid matters, is most manifest. In putrefying fish-material, on the contrary, this stage of the process is transient and difficult to seize. Water-breathing creatures expend proportionately less force than those that breath in air, their ternary substances, which constitute their combustive reserve of tissue store, is considerably less in quantity, the initial stage of hydrocarbonic fermentation is consequently very brief. Thus their putrefactive action, properly so-called, follows close on death. The same thing, however, obtains in man and the mammifera that succumb under violent exertion and exhaustion. In other respects the process is the same in both.

These remarks, however pertinent to the subject, enlighten us little in the lines of the enquiry. Without following further the details of putrefaction which are familiar, let us trace the indications of the concomitant changes the organised nitrogenous materials undergo in passing from their organic condition in the tissues to that of the organic alkaloids, so various in form and constitution. On this point there is still much to be learned. The action of the simpler kinds of ferments aids us little in the matter. The

residual products of the saccharine, for example, are few, the elements of sugar being few in number and simple in arrangement. The nitrogenous material of animal tissues, on the contrary, is very complex, the *débris* of its dislocations — its residual products — are, consequently much more numerous. Here we are groping, so to say, at our scientific limits. But if our knowledge of the mechanism of physio-chemical reduction is still very incomplete, by noting and associating indications, a general idea may be gained as to how the transformations are accomplished.

We know that the albumenoid element of living tissue-structures is distinctively next to insoluble in water, as becomes its function ; its solution in the form of fibrine in the blood or in albumen of the white of egg is only apparent. Almost completely insoluble in water, it is absolutely so in alcohol, such is its initial condition. The first step in the process of putrefactive destruction shows it to be soluble in water ; and mark, a similar process is partially, but continuously, going on in the tissues during life ; life being the equivalent of incessant tissue transformations, effete constituents in this way find elimination. On this first product classed as extracts soluble in water, follows a further

stage of degradation, affording us extracts soluble in alcohol. The alterations now accomplished are notable. The initial albumenoid characters, however, are not disposed of. The extract, soluble in alcohol, does not crystallise as yet, it persistently remains amorphous and refuses to combine with other chemical bodies. It still retains its complex constitution, consisting of carbon, hydrogen, oxygen, nitrogen, with traces of sulphur and phosphorus, but proportionately the constituent elements are different from what they were originally. In the main the proportion of oxygen has increased, while that of the others has diminished, precisely as if the albumenoid material had undergone oxydation or taken up one or more molecules of water. Analytically it is impossible to distinguish the two reactions; this however matters little. It is enough if we appreciate results which, when read aright, show that the process has been carried far below the initial stage and watery extract.

As the putrefactive process continues enriching and modifying in production, the extractive matter, soluble in alcohol, is followed by substances capable of crystallising in that menstruum: lucine, tyrosine, glycocolle, butaline, and the various organic compounds, and notably

the cadaveric alkaloids whose genesis we are now investigating. But the process of reduction still goes on ; the products become simpler, volatilise, as phenol or phenic acid, indol and skatol. Then follow those acids, volatile or fixed, of simplest constitution, such as the acetic, butyric, valerianic, and oxalic, in combination with ammonia simple or its compounds, which various ammoniacals are themselves the last residual product of the nitrogen, originally an element of the organic materials. The last stage of decomposition is now reached, and which need not be further followed.

As the condition under which the alkaloids originate must now be evident, a word or two regarding putrefactive signs, which sometimes mark the process of bacterial action and the presence of the alkaloid products, are needed. In the process of putrefaction, as in other fermentations, where bacterial action is aerobic, the gaseous effluvium is not fœtid. When it is on the contrary anaerobic, as in the lacto-butyric, for example, its presence is characteristic. The sulphur and phosphorus alluded to, attacked by the disengaged hydrogen, small quantities of sulphuretted and phosphoretted hydrogen are formed in the melange, imparting to it the familiar putrescent odour. It is then and not till

then that putrefaction is vulgarly supposed to take place. This is, however, incorrect. Odour is so constantly an accompaniment of decomposing nitrogenous material, that if it is absent the material is apt to be considered sound and suitable for consumption should it be alimentary. On scientific grounds the criterion is fallacious and liable to lead to dangerous results; injury to health of the consumer, and, occasionally, death itself is attributable to this cause. The generation of fœtid effluvia, it ought to be remembered, is but a secondary factor in the process of bacterial putrefaction. If its presence is characteristic of putridity, putridity may still be active in its absence, bacterides and poisonous alkaloids included. It is for the microscope and chemical analysis to decide the point.

En resumé, the phenomena of albumenoid putrefaction and alkaloid elaboration, being thus succinctly treated and exposed, the mechanism of the process which determines the formation of the alkaloids divests the question of its mystery, and we begin to see how substances, differing so widely in their chemical constitution, chemical properties and physiological action, may be similarly produced, and even realise the fact that any given alkaloid, irrespective of its class and order, may often have

several origins. It is not the original proteid substance that determines their position in the series. The simplicity or complexity of constitution of these alkaloid bases is all the more distinctive, according as the putrefactive process is more or less advanced. We have seen how the albumenoid constituents of the organic tissues comport themselves in earlier stages of bacterial destructive fermentation. In the more advanced we have also seen how the proteid molecule is, as it were, dissected by bacterial action ; how the lateral or associated chains of the cyclical nucleus successively disconnect themselves by fixing water, and then we see arise those unstable uric bodies so given to dissipate, those complex amidic acids which analysis detects in the putrid liquors precisely as it detects them when albumenoid material at 280° C. is reduced or dislocated with baryta, as has been shown by Schutzenberger in his beautiful researches. According to the stage at which the putrefactive process is experimentally expressed, we observe imperfect albumenoid molecules, cyclical nuclei which still retain some lateral chains in passing towards yet simpler forms. Hence, we have first those highly oxygenous alkaloids of M. Pouchet, then the less oxygenous diamines of Brieger, and

finally, when the putrefactive process is complete, the non-oxygenous pyridic alkaloids of MM. Gautier and Etard, the simplest of all.

A cadaveric alkaloid or ptomaine thus presents itself as the residual skeleton, as it were, of the proteid molecule which has undergone continuous disintegrative action, the ultimate terms of which are represented by the pyridic bases ; so that considered from a purely chemical point of view a ptomaine may be defined as the cyclical nucleus of a proteid molecule, that has undergone complete destruction in the process of putrefaction.

II.

Methods of Extraction.

THE putrefactive origin and serial elaborations of the ptomaine alkaloids, during the process of bacterial destruction having been examined, the means of extracting them must next be considered.

The methods devised and practised are very numerous. Almost all who are in any way authoritatively engaged with this department of scientific research, have either modified those long known, or wrought out new ones of their own. Selmi, and the Italians who have continued investigating on his lines, have operated according to the variously, if slightly modified, method of Stas. The form most used by the southern medico-legal experts and chemists, is that known as the Stas-Otto method. It consists in drenching to saturation hashed putrescent materials with alcohol 90° C., adding tartaric acid till acidulous reaction is appreci-

able. Sufficient time for digestion at a temperature of 70° to 75° C. being given, it is then allowed to cool, afterwards filtered and the residuum expressed. The operation repeated several times, the alcoholic liquids are collected and evaporated *in vacuo* at a temperature of 35° C. The liquid is then passed through a moistened filter to remove fatty matters, to dispose of other remaining impurities, and rapidly agitated with ether. Thus exhausted, the liquid is freed from the solvent, then it is mixed with powdered glass and evaporated *in vacuo* in presence of sulphuric acid, until it is nearly dry. The residuum is then drenched with pure alcohol, when it is allowed to macerate for twenty-four hours, and afterwards again evaporated *in vacuo* 35° C. The new residuum obtained is dissolved in a small quantity of water, to which is added bicarbonate of soda or of potash to alkalinity. The solution is agitated with four volumes of pure ether, then decanting and evaporating, the alkaloids remain as the residuum.

Other methods varied by the introduction of new solvents, such as chloroform; benzine and petroleum, have also been much used in Italy as well as in France and Germany. The best known is that which bears the name of

Dragendorff. It consists in first treating finely divided putrid meat with sulphuric acid diluted to 1-5th—15 cc. of acid to 100 cc. of clear bouillie of the hash, left to digest for some hours at 50° C.; it is then filtered and expressed; the residue is submitted to the same treatment. The liquids collected are then evaporated to a syrupy consistence, aud exposed in contact with alcohol at 93° C. for twenty-four hours; filtered and evaporated the residuum is then agitated with benzine and immediately decanted. The operation is repeated, ammonia is added to the residuum till alkaline reaction ensues. It is then heated to 40° or 50° C., when it is again exhausted with benzine. By several repetitions we obtain a certain quantity of benzine holding in solution impure alkaloids; this is purified by converting it into sulphates, decomposing with ammonia, recovering with suitable dissolvents and submitting to treatment similar to what we have just described.

The alkaloid extracts obtained by the above described or indicated methods, certainly enable operators to utilise alkaloid reagents with some degree of success. The products responding to ordinary tests are reliable in physiological experimentation, still, it is to be observed that, in separating the alkaloids from the extracts

which they accompany by this method, it is only possible, and with the utmost care, to obtain even impure bases, in quantity sufficient to admit of isolation and correct analysis. Consequently, no product obtained by those methods of procedure has been defined, differentiated or physiologically tested in a sufficiently conclusive manner.

M. Pouchet, who in 1880 succeeded in isolating from the normal urines an alkaloid fixed and toxic, later on adapted a method which consisted in precipitating these bodies in solutions slightly alkaline, by adding an excess of tannin, and then decomposing the tannates formed with the hydrates of lead in the presence of alcohol. The evaporation of the alcoholic solution leaves a syrupy mass which can be dialysed ; the bases are to be found in the dialysed portion of the solution, when they can be separated with such solvents as ether, chloroform, or petroleum. Although Pouchet obtained excellent results, in fact, discovered two new alkaloids, which he analysed, by this mode of operating, it is not to be commended in less experienced hands. As M. Gautier points out, the tannin is very liable to oxydise and deteriorate in the presence of alkalies, and only precipitates them very imperfectly, especially on exposure in conducting operations.

It is only so recently as 1881, that MM. Gautier and Etard entered on the study of the products of putrefaction of the albumenoids; researches which were continued until 1883. In this important inquiry the material selected for operations consisted for the most part of the putrid *débris* of the horse, ox, fish, and shell fish. In the course of investigations, the first that had been conducted in a strictly scientific manner, the methods adopted of separating the ptomaines were somewhat different from those already described. The putrescent liquors were sparingly acidulated with sulphuric acid, agitated, relieved of supernatant fats and oils, and finally distilled *in vacuo*; the syrupy residuum relieved of its crystals was rendered alkaline with baryta, filtered and exhausted with chloroform, which dissolved the bases: the excess of chloroform was evaporated *in vacuo*, or in a current of carbonic acid gas, care being taken to prevent access of atmospheric air, or elevation of temperature which might destroy the bodies sought for. The remaining liquor after the removal of the chloroform was treated with water and tartaric acid, which separates a brownish resin from the liquor; the latter treated with potash disengages a pungent odour of the carbylamines, whilst the ptomaines are

set free: these are taken up with ether which is disposed of by evaporating under reduced pressure *in vacuo* and in presence of caustic potash for the purpose of preventing carbonisation.

By submitting the bases thus obtained to distillation or fractional precipitation by the aid of chloride of platinum, or, if in sufficient quantity, by distillation *in vacuo*, they can then be methodically separated.

It is well to mention that Gautier has not continued the above process. He has returned to the method of his earlier operations, and it is that he now makes use of with little alteration. Sulphuric acid is no longer employed. To the alkaline liquors of precipitation, he adds oxalic acid to acidulation, allowing them to rest so long as fatty acids form, and which, as they come to the surface, are separated. By filtering and distilling, the liquors are freed from pyrol, skatol, phenol, indol; the volatile fatty acids and a portion of the ammonia are disposed of. He then alkalises the undistilled portion with chalk; separates the precipitate which forms and which contains the greater part of the fatty acids; distils the alkaline liquors to dryness *in vacuo*; and collects the vapours in very weak sulphuric acid, which retains the ammonia and the volatile bases. In order to neutralise the liquor

of distillation, it is evaporated nearly to dryness and the ammonia sulphate removed, treating the remaining mother-liquor with pure concentrated alcohol ; this dissolves the alkaloid sulphate and leaves the ammoniacal sulphate. The alcohol removed, the solution is decomposed with an alkali, and the ptomaines set at liberty and taken up with ether, chloroform, or petroleum.

The latest method deserving notice is that of Brieger ; though the last it is certainly not the least in importance and is as follows :—Flesh material is set aside to putrefy for some days in contact with water. The mass is then boiled, then filtered, then precipitated with the subacetate of lead. Excess of lead is removed from the liquor with sulphuretted hydrogen ; freed from the sulphides of lead and evaporated to a syrupy consistence, and exhausted with amylic alcohol, the residuum is treated with water ; this is concentrated, acidulated with sulphuric acid and washed repeatedly with ether to get rid of the oxy-aromatic acids. The liquor by evaporation is reduced to one-fourth of its initial volume in order to separate its fatty acids ; the sulphuric acid is taken up with baryta, and the excess of baryta with anhydride carbonic. The liquor is then filtered and heated in a water

bath; when cooled, it is precipitated with chloride of mercury. The precipitate wash is then decomposed with sulphuretted hydrogen, finally concentrated by evaporation. Organic substances are first deposited, which are separated and washed in pure alcohol. Very soon long needle-shaped crystals are seen to form, which are soluble in water and weak alcohol, insoluble in pure alcohol, benzine, chloroform, &c.

The bodies which crystallise are afterwards separated the one from the other by fractional precipitation with the aid of chloride of platinum or chloride of gold.

It may be well to note that Brieger has recently somewhat simplified his process. The putrid liquids are brought to the boiling point, filtered, then immediately precipitated with chloride of mercury. The liquors are then precipitated by treating them separately with sulphuretted hydrogen; these furnish the products which are isolated as before.

III.

Chemical Properties.

It is well to be reminded that Selmi never succeeded in obtaining alkaloids in sufficient quantities for analysis, or to enable him to ascertain their constitution and place in the family of bases already known. It was not until between 1881 and 1883 that Armand Gautier and his associate, M. Etard, first determined their precise analysis. It was then they, for the first time, recognised that of these substances, those that were found in great abundance and constituted the alkaline products of bacterial putrefactive processes in their completion, form two distinct series, the one pyridic, the other hydropyridic. At this time there was only one example of the former known. What was more particularly due to Selmi was the numerous determinations in the examination of small quantities by reagents of various kinds. It is the determinations of Selmi, Gautier, and others, that we will now proceed to summarise.

Having traced historically the course of investigation followed by various workers in the putrefactive field, the qualities of the peculiar alkaline basic products have only been incidentally alluded to, it will now be necessary to complete the examination of their properties.

The ptomaines are bases solid or liquid, very alkaline and which combine with strong acids, not as the amines, the salts of which are disassociated by water, do, but in the same manner as the powerful metallic bases. They absorb to saturation the strong acids, sometimes attracting carbonic acid of the atmosphere. According as they are solid or liquid in their properties, they differ in many respects, so much so that they come under two categories, as in the case of the vegetable series of alkaloids. The bases of the one class, liquid, volatile, and of an odour, *sui generis*, contain no oxygen; those of the others are oxygenous, solid, and crystalline.

The liquid ptomaines possess a virous, cadaveric odour, occasionally suggestive of musk or odoriferous plants. It is possible that between the products of bacterial putrefaction of animal tissues and the perfumes of vegetable cells of flowers, similarity is not altogether accidental. As M. Gautier surmises, the resemblance has

a deeper basis of reality than might at first appear. The liquid ptomaines are soluble in alcoholic ether.

The solid ptomaines are white, generally crystalline, very soluble in water, insoluble in liquids such as alcohol, benzine, chloroform, which readily dissolve substances rich in carbon. The solubility of these ptomaines is, however, disturbed by the presence of impurities, and amylic alcohol which dissolves but slightly pure neuridine, for example, on the contrary, dissolves it in notable quantity when the bases are blended with extractive matters.

The chemical reactions are common, at least, for the most part to the two categories. All the ptomaines are isolable : they combine with acids ; an excess of acid decomposes them, imparting at first a rose colour which becomes in precipitation a resinous brown. They all combine in a state of chloro-hydrates with chloride of platinum, and form double salts which are more or less crystallisable. An excess of chloride of platinum decomposes them ; decomposition is, however, effected by a great number of reagents ; light of itself effects it.

In general the ordinary alkaloid reagents precipitate the ptomaines ; the chloride of gold, the double iodides of mercury and potassium,

the iodides of bismuth and potassium, the reagents of Nessler, Froude, Schultz and Sonnenschein, picric acid and tannin.' The chlorate of mercury does not always precipitate them, but it frequently combines with the ptomaines to form the crystallisable double chlorides, which Brieger has frequently utilised in his researches in separating the obtained alkaloids one from the other. All the alkaloids are not precipitable by all the enumerated reagents; only one solitary body acts on all without exception, that is, phosphomolybdic acid.

Before the isolation of the alkaloids of putrefaction in a pure state had been achieved, the colour reactions which served to indicate their presence, had more importance attached to them than is awarded them to-day. Selmi had ascertained and confirmed the fact, that hydrochloric and sulphuric acids, simple or combined, developed, especially when heated, a red colour by acting on the bases of putrefaction. When a ptomaine is heated with nitric acid and afterwards saturated with potash, a beautiful yellow colour is developed.

The ptomaines by virtue of their oxydisability ought to act as energetic reducing or decomposing agents in a great number of reactions. Not only are the chromic and iodic acids

decomposed by them, but so also is the nitrate of silver. Furthermore, the bromide of silver and frequently the ferricyanide of potassium which, transformed in contact with ptomaines into ferricyanide, gives with the salts of iron the Prussian blue. MM. Brouardel and Boutmy regarded this reaction, first observed by Selmi, as a means at once simple and of general application in distinguishing the alkaloids of vegetable origin from those of animal putrefactive origin. Unfortunately, many of the vegetable and artificial alkaloids decompose the ferricyanide and ferric-chlorides. Gautier has clearly shown that of the alkaloids, there are many that do not decompose the ferricyanide, as anemonine, peltierine, sabadelline, &c. ; other alkaloids reduce slowly and feebly, and among them veratrine, igasurine, colchicine, nicotine, emetine, hyosciamine and apomorphine.

Thus we see some of the artificial or natural vegetable alkaloids comport themselves exactly as the ptomaines do by decomposing instantaneously the melange of ferricyanide of potassium and ferrichloride. This class is numerous, and comprehends among other bodies pyridine, isodipyridine, collidine, naphtylamine, toluidine, diallylene-diamine, morphine, atropine ; also the alkalies acetonic, aldehydic, &c. The reduc-

ing or decomposing power is far from being a characteristic special of, or peculiar to, the ptomaines. Many of them, according to M. Pouchet, do not even possess it at all; and Brieger affirms that he has never observed it in the case of the pure oxygenous ptomaines. He attributes the reduction observed by Brouardel and Boutmy to the presence of peptones which vitiate their products. This view is certainly extreme. If we consider the construction of the hydropyridic bases, it is easy to conceive the energy of their reductive action in the process.

This admitted from all that has been stated, it must frankly be conceded that the reactions of the ptomaines present the closest analogies to those of the vegetable alkaloids; that the two intimately related classes of bodies possess analogous properties, and that the general reagent which distinguishes the one group from the other still remains to be discovered.

IV.

Classification and Definitions.

The ptomaines are divided into two classes, the non-oxygenous and oxygenous, which may be studied apart. First come the pyridic bases of Gautier, or those ptomaines which, besides being the most abundant, persist throughout the whole of the putrefactive process.

Non-Oxygenous Alkaloids.

Parvoline $C^9H^{13}N$. — This was the first ptomaine chemically analysed and defined. It was discovered by MM. Gautier and Etard in the putrefactive products of the mackerel and horse flesh, by means of the ordinary method and operating on the chloroform extracts. It is described by them as an oily base of an amber colour and May odour, boiling a little below 200° C., slightly soluble in water, very soluble in alcohol, ether and chloroform ; it resinifies readily on exposure to the air. Its chloroaurate

is soluble, its chloroplatinate is little soluble, it crystallises in flesh colour, intensifying on exposure.

In heating to 200° C. in a closed tube the crude product of the reaction of ammonia on propionic aldehyde, Waage has obtained a base $C^9H^{13}N$, boiling at 193° to 196° C., and which has the closest resemblance to the parvoline of putrefaction.

Hydro-Collidine $C^8H^{13}N$.—This base has also been obtained from the putrefactive products of the mackerel and horse, and even ox flesh. It is an almost cloudless liquid of slightly oleaginous consistence, of a seringous odour, boiling at 210° C. without alteration of density, which at zero C. is equal to 1.0296. It oxydizes on exposure, becoming viscous and dark in colour; it fixes the carbonic acid of the atmosphere.

The chloride of gold forms with the hydro-collidine a chloride very soluble but unstable which decomposes readily when cold. The instability of the double salts of the hydro-pyridic bases is characteristic of this. MM. Cahours and Etard, however, treating nicotine with selenium, have obtained a dihydro-collidine of $C^8H^{13}N$, boiling at 210° C. On the other hand, Œchsner de Connick, in treating

in a closed vessel with phosphorus and hydroiodic acid, the collidine which he had discovered in products resulting from the action of potash on cinchonine and brucine, has accomplished the synthesis of a dihydrocollidine presenting close affinities with the base of MM. Gautier and Etard.

The ptomaine hydrocollidine is very poisonous, even in very small quantities.

Base $C^{17}H^{38}N^{4}$.—The mother liquors of the platinichlorides of the presiding bases are capable on concentration of yielding flesh-coloured crystals decomposible at 100° C. with distinctly flowery odours. The analysis which MM. Gautier and Etard have made of this chloroplatinate enables them to establish the formula $(C^{17}H^{38}N^{4}2HCl)$ PtCZ.

Base $C^{10}H^{15}N$.—This ptomaine was discovered in 1883, by Guareschi and Mosso, who isolated it by the Gautier-Etard method from the putrid febrine of the bullock. And so late as 1886, it has also been detected among the basic products arising from the putrefaction of the cephalopode pulps common to the shore of the Mediterranean. This base is very alkaline, of pyridic odour, little soluble in water, and readily resinifiable. It is precipitated by chloride of gold, chloride of platinum and

corrosive sublimate, tannin, picric, phosphotungestic, and phosphomolybdic acids ; with the ferricyanide of potassium and the salts of iron it furnishes prussian blue.

This ptomaine is probably a pyridic base, perhaps a new corindine, according to Œchsner de Connick, the superior homologue of the parvoline of MM. Gautier and Etard.

COLLIDINE $C^8H^{11}N$. — Was extracted by Nencki, in 1876, from the putrefactive products of 600 grms. of gelatine and 200 grms. of bullock pancreas to 10 litres of water. The discoverer has not identified it with the collidine of Anderson, the synthesis of which Bæyer and Ador accomplished by heating the aldehydrate of ammonia to 120° C., in contact with urea. Nencki considered that ptomaine as an isophenylethylamine.

$$C^6H^5—CH\begin{cases} CH^3 \\ NH^2 \end{cases}$$

Seemingly, however, this base only arises under the conditions Nencki has indicated. If the gelatine is allowed to putrefy without the previous addition of pancreatic tissue, according to Brieger no trace of collidine is to be found.

NEURIDINE $C^5H^{14}N^2$.—This base is one of the most constant products of the putrefaction

of albumenoid substance. The ptomaine was discovered in 1884 by Brieger, who has since detected it in the putrescent matters of flesh, fish, decaying cheese, &c. From the organic structures of the human body, it has also been obtained by his method already described. This base is only known in the form of a salt, or in combination with the chlorides of gold or platinum. If we try to isolate it from its chlorohydric combination by the aid of the moist oxyde of silver, a gelatinous amalgam is obtained which readily decomposes.

The salts of neuridine, the chlorides of gold and platinum in particular, are well crystallized. The chlorohydrate is precipitated by phosphotungestic, phosphomolybdic, picric acids, by the reagents of Schultz, the double iodides of bismuth and potassium.

Soda in solution breaks up the chlorohydrate of neuridine into a melange of dimethylamine and of trimethylamine.

Chemically pure neuridine is not toxic.

CADAVERINE $C^5H^{16}N^2$.—In bodies subjected to prolonged putrefaction, Brieger has met with a base very difficult of purification, and to which he has given the name of cadaverine. Bœcklisch has separated it from herring brine, and quite recently—1884—the alkaloid has been detected in marine cephalode pulp.

It is a colourless liquid somewhat viscous, boiling at 115° to 128° C., and of the disagreeable odour of the conicine character. It absorbs anhydride carbonic, and forms with the acid definitely crystallized salts insoluble in ether and alcohol. In contact with this base, the melange of ferricyanide and ferrichloride gives feebly the bluish tint ; ordinary alkaline reagents precipitate the ptomaine. Heated with potash and chloroform, cadaverine does not give carbylamine. Dissolved in methylated spirit, it fixes the iodide of methyl and gives a hydriodate of dimethylcadaverine $C^5H^{14}(CH^3)^2N^22HI$. Cadaverine gives with the chloride of gold a double salt, and with chloride of platinum a chloroplatinate bright red orthorombic crystals. The ptomaine is not toxic.

PUTRESCINE $C^4H^{12}N^2$.—Like the preceding ptomaines is obtained from the flesh of the mammifera and herring brines. It is a limpid, slightly oily liquid, the odour of which resembles that of sperm and reminds us of the pyridic bases. It boils at 135° C., and with difficulty evaporates with the water. The very powerful base presents the reactions of the vegetable alkaloids, attracts the anhydride carbonic from the atmosphere, and gives with the acid salts in well defined crystals. Its bright microscopic

crystalline pellets are little soluble in water, and much resemble cholestrine.

The chlorohydrate of putrescine gives with nitrate of potash a denitrilized derivative, which may perhaps permit putrescine being regarded as an ethylenedemethyldiamine

$$C^2H^4 < \begin{matrix} NH.CH^3 \\ NH.CH^3 \end{matrix} = C^4H^{12}N^2.$$

Putrescine is not toxic.

Mydaleine.—In the mother liquors from which the preceding bases have been isolated owing to the varying solubility of their chloroplatinate there remains a toxic alkaloid which has also been isolated, but in too small quantities to permit of its complete study. The analysis of it is suggestive of a diamine similar to those we have been dealing with.

The action of mydaleine on the animal economy is very interesting, as will be seen when we come to treat of the physiological properties of the ptomaines in general.

Oxygenous Alkaloids.

These bases serve as the connecting link between the ptomaines and the leucomaines. With the exception of gadinine they are to be

met with in the normal tissues as well as in putrescent animal materials.

$$\text{Neurine } C^5H^{12}N\,(OH) = \begin{matrix}(CH^3)^3 \\ C^2H^3\end{matrix} > N{-}OH.$$

Hydrate of trimethylvinylammonium.

It is known that the breaking up of a complex compound with a watery solution of baryta, the lecithine present in the animal economy, by taking up or fixing the water, furnishes besides phosphoglyceric and stearic acids, and a base choline $C^5H^{13}NO^2$ the synthesis of which Wurtz effected in treating trimethylamine with oxyde of ethylene in the presence of water

$$\begin{matrix}CH^2 \\ CH^2\end{matrix} > O + (CH^3)^3N + H^2O = \begin{matrix}(CH^3)^3 \\ C^2H^4OH\end{matrix} > N.OH$$

This synthesis characterises choline as the hydrate of trimethylhydroxethylene-ammonium. Treated with hydriodic acid choline is converted into an iodide of iodethylene-trimthylammonium

$$\begin{matrix}(CH^3)^3 \\ C^2H^4OH\end{matrix} > N.OH + 2HI = 2H2O + \begin{matrix}(CH^3)^3 \\ C^2H^4I\end{matrix} > N.I.$$

The oxyde of silver transforms this latter body into a new base neurine which is a hydrate of trimethylvinylammonium.

$$\left.\begin{array}{l}(CH^3)^3\\ C^2H^4I\end{array}\right\rangle N.I + Ag2O = 2AgI + \left.\begin{array}{l}(CH^3)^3\\ C^2H^3\end{array}\right\rangle N.OH.$$

This is the neurine that has been met with by Brieger in the products of cadaveric putrefaction, when it arises from the breaking up of lecithine. It is a syrupy base soluble in water in any proportion, strongly alkaline ; its chloroplatinate well crystallized may be removed from the mother liquors of the neuridine. This base is toxically interesting.

CHOLINE. $C^5H^{15}NO^2 = \left.\begin{array}{l}(CH^3)^3\\ C^2H^4{-}OH\end{array}\right\rangle N.OH$

Hydrate of trimethylhydroxethylenine-ammonium.

It is Stricker who has isolated this body from the bile. It is distinguished from neurine by the composition and formula of constitution as given above. The choline is a base which is elaborated both during normal life of the tissues, and during their bacterial destruction, and is, therefore, both ptomaine and leucomaine. Brieger has isolated it by crystallizing in the form of picrate of choline in the mother liquors from which he derives the neurine.

Choline is a syrupy liquid soluble in water,

very alkaline, which unites with acids giving salts in well defined crystals. The chloroplatinate being less soluble in water than the salts, than the corresponding salts of neurine, this property indicates the method of separating the two bases so similar and so often blended together. Heat splits up choline into glycol and trimethlamine $C^3H^{13}NO = C^2H^6O^3 + (CH^3)^3N$; is that doubtless which explains the presence of trimethylamine in the products of a great number of putrefactions.

The ordinary alkaline reagents precipitate both choline and neuridine. They do not reduce the ferricyanide and ferrichlorides.

Choline is less toxic than the neurine.

MUSCARINE $C^5H^{13}NO^2$ was discovered by Schmiedberg and Koppe in the toadstool,—*agaricus muscarius.* Schmiedberg and Harnack have accomplished its synthesis by oxydizing choline with nitric acid; this permits muscarine to be regarded as an aldehydic alkaloid.

$$\begin{matrix}(CH^3)^3 \\ C^2H^3O\end{matrix}\!\!>\!N.OH.$$

Brieger has isolated it along with ethylenediamine in putrid fish meat. Muscarine is

found present in the mother liquors, in which the chloride of platinum has precipitated the ethylene-diamine.

The muscarine is a solid crystalline deliquescent substance, which plays the *rôle* of a powerful base, attracts carbonic acid gas from the atmosphere and is precipitated by the ordinary alkaloid reagents, and gives with the choloride of platinum and chloride of gold crystalline compounds. Its aldehydic constitution explains, as Professor Gautier has shown, why it reduces the melange of ferricyanide, ferrichloride.

Muscarine is a violent poison.

GADININE $C^7H^{16}NO^2$.—Brieger obtains this body at the same time and along with the preceding base from the cod-fish—*gadus callarius*—in process of putrefaction. This alkaloid has not been isolated in a free state. The chlorohydrate of gadinine crystallizes in colourless needle-shaped prisms, is soluble in water, insoluble in alcohol, and does not combine with chloride of gold, but gives with the chloride of platinum a yellow chloroplatinate. It is to be remarked that the base only differs by additional H, from the composition of an aminoœnanthylic acid.

Its salts are not toxic.

BASES $C^7H^{18}N^2O^6$ and $C^5H^{12}N^2O^4$.—M. G.

Pouchet has published since 1880, quite a series of interesting works on the ptomaines. He endeavours to isolate by a somewhat similar method to that of Stas and Dragendorff, the alkaloids of the residuary liquors resulting from its industrial treatment of bones, flesh and *débris* of every kind, by dilute sulphuric acid. He has been enabled in this manner to extract from the material two alkaloids, which the unequal solubility of their chloroplatinates in alcohol admits of being separated.

The base $C^7H^{18}N^2O^6$ is formed of thick short prisms very readily alterable. The alkaloid $C^5H^{12}N^2O^4$ is needle-shaped, arranged in pencil form, and appears to alter even less readily.

The ordinary alkaloid reagents precipitate these two ptomaines. The precipitate obtained by phosphomolybdate of sodium is reduced, and in presence of ammonia gives the blue tint. It is known that aconitine presents the same reaction.

These two bases are toxic.

In the course of his researches, Brieger has detected other alkaloids less defined or simply indicated, but which are now receiving his careful study. Nothing more need be said of them until investigations are complete. The same applies to those ptomaine extracts, and

the various impurities of cadaveric putrefaction characterised only by colour reactions and some physiological properties.

V.

Physiological Actions.

If the toxic actions of the alkaloids of putrefaction remain to be considered, it must be without pretention to completeness or precision ; the present position of their history does not permit of that. It may be affirmed that some are powerfully energetic, others almost inert. In general terms, they must be accepted as poisonous, and their mode of action on the animal economy much the same as that of the hydropyridic bases. Their effects, however, while presenting certain characters in common, vary according to their class or group. Consequently the physiological actions of the ptomaines supplement the chemical history, and form an introduction to their medical toxicology.

The difficulty of isolating them in quantity sufficient for the separated study of their effects physiologically, has made it necessary to employ the ethereal, chloroformic and alcoholic extracts for this purpose. By converting these

into chlorohydrates, sulphates, &c., salts more or less impure, their actions and effects have been carefully observed. Sensibly, the free ptomaines smell virous or cadaveric. When free from oxygen they have a virous odour similar to that of conicine or pyridine, sometimes aromatic and agreeable resembling musk, orange flower or camilla, &c. They are bitter to the taste, and for the most part piquant, benumbing the tongue and palate, and give rise to a sense of constriction of the throat.

The memoirs of Gautier and Corona will perhaps supply the most instructive illustrations as regards such properties. Let us cite the series of experiments undertaken with ptomaines, derived from a dead body exhumed four months after interment.

Ptomaines Extracted by Ether.—One gramme of the aqueous solution injected into the skin of a dog of medium size induced, after twenty minutes, irregular contraction of the pupil, convulsive tremblings, increased heart's action, congestion of the external ear, slight increase of temperature; the animal became languid. Forty minutes after injection, there appeared spasmodic action of the facial muscles and limbs, diminished respiration; death in forty-four minutes. On opening, the thorax

showed immobility of the auricles, irregular contraction of the left ventricle, right side filled with blood, left side empty.

Observations on the frog were somewhat similar.

PTOMAINES EXTRACTED BY CHLOROFORM.—The hydro-alcoholic solution of the alkaloid was injected hypodermically into a dog of medium size. Almost immediately respiration rose to 100 and 134 a minute, heart's action increased with heat and congestion of ear helices, normal state recovered in about twenty minutes. The effects on the frog were slight agitation, flaccidity of the muscles and loss of motor power under galvanic current, nervous sensibility maintained, but no contractility elicited when the electroid was not in direct contact with the muscle or muscles themselves.

PTOMAINES EXTRACTED BY ALCOHOL.—Subcutaneous injection induced in the case of the frog confused movements, irregular dilatation of the pupil, loss of cutaneous sensibility, followed with general muscular relaxation.

From these experiments, and others too numerous to mention, these authorities conclude as follows :—The cadaveric alkaloids are in general venomous to a high degree. The free ptomaines are more energetic than their

salts, those that are soluble in silver more particularly. On frogs the principal phenomena observed are as follows :—I. Dilatation of the pupil followed with contraction ; II. Tetanic convulsions followed with muscular flaccidity ; III. Diminished respiration and increased heart's action ; IV. Total loss of cutaneous sensibility.

On the dog the phenomena observed are : I. Irregular contraction of the pupil passing to contraction ; II. Marked heat and injection of the ear helices from paralysis of vaso-motor ; III. Diminished respiration ; IV. Somnolence soon followed by convulsions and death ; V. Loss of muscular contractility to electric stimulus.

In these experiments the loss of muscular contractility, even in the presence of the electric stimulation, is very remarkable. The peculiarity associates the ptomaines with the poisonous alkaloids of the mushrooms and with the muscarine in particular, which Brieger has since detected in certain putrefactions. This fact M. Gautier observed earlier than Selmi, Corona or Brieger. Corona, on the contrary, differentiated the ptomaines from some other alkaloids, for example, the curara, which leaves the muscle its contractility under the influence of the electric current, or sulpho-cyanide of potassium, which, it is true, destroys the con-

tractile property in the presence of electric stimulation, but leaves it not flaccid, but in spasmodic tension.

Two experiments of Gautier made with the base, not altogether pure, answering to the formula $C^8H^{13}N$—hydrocollidine—are interesting to note.

First, 0.007 grme. quantity injected under the skin, beneath the wing of a small bird. In two minutes ruffling of the plumage and vomiting were excited, followed with loss of motor co-ordination, paralysis, convulsions and death in fifty minutes after injection.

Second injected under the skin of small bird of the same species, 0.0017 grme. of same base, but purer in quality. In two minutes, creature loses co-ordinating power, turns over on its side, flutters, unable to recover balance, paralysis increases with loss of sensibility, death in fifty minutes after injection.

According to M. Gautier's experiments on the action of snake poisons, this base would seem to be almost as powerful as the venom of the *corbra di capella*. He has shown that a milligramme of that virus kills a sparrow in about sixty minutes; as in the preceding instance, there is paralysis of the posterior tract, immobility; but with the cobra venom we

observe the panting, violent agitation, and after death heart at systole and free of blood.

We have seen that the ptomaines of M. Pouchet are oxygenous. Their action on animals has been studied much more closely than that of the preceding bases. The two alkaloids which he has studied are energetically toxic on frogs, killing them rapidly, and producing torpor and muscular paralysis, with abolition of the reflexes ; after death heart at systole.

Several of Brieger's bases are also toxic. They have been so characterised, but the effect which they gave rise to are but little known. Mydaleine excites profuse diarrhœa, vomiting, intestinal inflammation ; the heart after death at diastole. One of the bases, we have said, is identical with muscarine. Neurine itself is very toxic ; a few milligrammes suffice to kill a cat. It excites abundant secretions, diarrhœa, accelerating respiration and convulsion before death.

VI.

Medico-Legal Import.

Toxicology brings us in contact with the practical side of ptomaine investigation, that on which its greatest value depends. Though researches are numerous and the literature of the subject considerable, it must be confessed it yet leaves much to be desired. Investigations still in progress, and others incomplete, obscure the subject, and if they do not disarm the medicolegist, render correct differentiation at once delicate and difficult.

In the introductory historical notice, reference has been made to the impetus given to this phase of the subject, by the evidence of Selmi in Italy and Otto in Germany, in two celebrated cases of criminal poisoning. Enabled by previous researches to detect the presence of ptomaine alkaloids in both instances, these eminent toxicologists contested the conclusions of the experts for the prosecution with complete success. Scientific attention being much

excited by these facts, numerous publications under various titles appeared; researches, colour reactions, physiological and chemical properties, &c., all relating to cadaveric extracts whose chemical compositions were as yet unknown or ill-defined. As a great portion of these data must, therefore, be treated with caution and reserve, we select a few of the most reliable results, beginning with the analyses of experts, who have found themselves in the presence of organic alkaline bases, which they were unable to identify with any known alkaloids.

In the examination of putrid bodies of subjects, who were known to have died from natural causes, Selmi succeeded in extracting by ether from aqueous alkaline solutions, an alkaloid which the chloride of mercury precipitated in white; sulphuric acid coloured it violet; a melange of sulphuric acid and dichromate gave a greenish and phosphomolybdic acid a bluish tint. The base reduced iodic acid, and was precipitated by the chloride of gold. In following the same method, but in employing other solvents, Selmi succeeded in isolating other substances which were only definable in his hand by colour reactions.

In the course of another medico-legal examination, Lieberman obtained from the stomach of a subject in a state of putrefaction, by

the Stas-Otto method, a substance similar to conicine, but differing from this base in two properties—it was neither volatile nor toxic; that cadaveric conicine was precipitated in white by tannin, in brown by iodized iodide of potassium, in yellow by phosphomolybdic acid, and again in white by aqueous solution of chlorine and the perchloride of mercury.

Van Gelder, another medico-legal expert, has extracted from various portions of a dead body, which contained arsenic, a brownish residue which chlorine solution, Meyer's test, perchloride of mercury and tannin precipitated in white, the chloride of gold and platinum in yellow.

In 1880, Spica published an interesting observation which deserves attention. Called upon to examine the liquid taken from the dead body of a woman, the subject of extra-uterine fœtation, he applied the method of Dragendorff. Exhausting the residue of his operation with the solvents ordinarily employed, Spica obtained with the aid of chloroform an amorphous base, probably impure, which gave with the iodized iodide of potassium a red precipitate soluble in excess of the reagents, with a chromic melange a yellow precipitate, which finally became green; with the test of Meyer a white cheesy precipitate was

given. That alkaloid, when injected into the subcellular tissue of a frog, induced dilatation of the pupil and increased respiratory action, and death in forty minutes.

The same year, 1880, Gianetti and Corona were commissioned to seek for poison in the body of a young man. They obtained by exhausting with various solvents the residuum furnished by the Stas-Otto method, a quantity of alkaloid material. They isolated roughly several ptomaines of different odours, which bases were very alkaline, and gave with the solution of iodine in hydriodic acid, a brownish precipitate, with the chloride of platinum a precipitate of a cannella colour; their chlorides underwent reduction when cold, converting into prussian blue the ferricyanide of iron.

The toxic action of these ptomaines presented the phenomena frequently observed in similar instances. In injecting them hypodermically, they determined pupilar dilatation, followed with contraction, convulsions controlled the heart's action, and after a little complete loss of cutaneous sensibility followed.

To Brouardel and Boutmy we are indebted for the following observations on a body eighteen months in water. In this instance, by Stas's method fixed alkaloids were detected that

responded to the various tests—Meyer's to begin with—precipitating with potash, reddening with sulphuric acid and ferri-oxyde of baryum, colouring to brick red when cold, violet when hot ; the base gave prussian blue with ferricyanide of potassium and the salts of iron. Its toxic action resembled that of veratrine. In another instance, but under different circumstances—the subject having died asphyxiated with carbonic-oxyde was preserved for several days at a low temperature—no traces of alkaloid were to be detected. By increasing the temperature putrefaction thoroughly declared itself, when a fresh examination proved perfectly successful. An alkaloid was then met with which sulphuric acid coloured brown and Meyer's test precipitated. Again the same toxicologists had an opportunity of carrying out ptomaine researches in the *débris* of a stuffed goose too long kept, which poisoned some dozen persons, with fatal effect on one. The organs of this victim being likewise submitted to examination by the experts they were enabled to extract an alkaloid liquid that smelled of mice-piss, and whose reactions were characteristic of the alkaline bases of vegetable origin, of conicine in particular. Such examples might be multiplied, but no more are required to

strengthen the following legitimate conclusions. Firstly, that in the bodies of persons who have died a natural death, the methods of Stas and Dragendorff were capable of detecting the presence of toxic alkaline compounds possessing properties resembling those of the well-known vegetable alkaloids. Secondly, that the quantity of those alkaloids becomes the more appreciable as the process of decomposition advances.

In the aforementioned examples from experts, we have intentionally avoided giving conclusions or noting reactions on which might be based a differentiation of ptomaines and alkaloids that might have been criminally introduced during life. The question now comes, is this possible? Is there any general reliable and positive procedure applicable in all cases; or must we, on the contrary, have recourse to special chemical and physiological reactions? In other words, has the discovery of the alkaloids of putrefaction outrun the current medico-legal resources and criteria?

The question is most important, and it was with a view to its solution that the Italian commission of 1880, under the presidency of Selmi, and after his death under that of Canizzaro, was issued. In his voluminous reports Marino

Zicco, who contributed so industriously, attributed to neurine and choline alone the chemical and physiological reaction with which the ptomaines were being credited ; he also attributed the origin of neurine to the splitting up of lecithine from the action of the sulphuric acid used in researches by the Dragendorff method. This point, among others, the labours of Gautier and Etard conclusively disposed of. Nevertheless, the labours of the commission furnished data of much value in elucidation of the points submitted for solution.

As has already been stated in dealing with the chemical characters of the alkaloids, the reducing action of the ptomaines on the ferricyanide of potassium in the presence of the ferric salts and the resultant prussian blue, has not the general characteristic application that either Brouardel or Boutmy had at first awarded to it. M. Gautier has clearly shown that that reaction is not peculiar to the putrefactive alkaloids ; according to Pouchet and Brieger a certain number of ptomaines do not give even an indication of it.

M. Hugounenq of Lyons, who has so clearly and concisely resumed the medico-legal dilemma, notices the complex reagent which Wefers, Bettenk and Van Dessel have recently

proposed. This is a combination of hydrochloric acid, chloride of iron, chromic anhydride, and ferricyanide of iron. This, it was alleged, gave prussian blue with all the ptomaines, while morphine alone of the vegetable alkaloids was capable of yielding it. Brieger, however, was unable to verify this reaction in the case of any of the alkaloids discovered by him. There is, then, no common method by which in every case any given vegetable alkaloid can be distinguished from any given ptomaine. A particular alkaloid, however, may be distinguished from a ptomaine by a series of particular features. As they are of the utmost importance, we refer those practically engaged upon the subject to M. Gautier's contributions ; their consideration forms an invaluable page of his masterly *mémoire ;* from the nature of the present study what is required of us is merely to indicate them.

As may be known, the object of the Italian Ptomaine Commission was not so much the investigation of the nature and existence of these alkaloids, as determining whether medico-legally their presence might give rise to gross miscarriage of justice from expert misapprehension. As those bases, fixed or volatile, of cadaveric materials might be readily confounded

with other toxic alkaloids, animal or vegetable, it was necessary to avert judicial error, and also to determine those ptomaines which some insisted on identifying with bases already known, more particularly with neurine. Selmi was the first to give warning, noting at the same time the difference between that alkaloid—though admittedly impure, detected as pyridic by M. Gautier—and conicine. If Marino Zicco did not do this, he showed by his researches that alkaloids of putrefaction were always minute in quantity, that it was possible to distinguish those ptomaines from a great number of vegetable alkaloids when introduced in the system during life, and that ptomaines, and particularly neurine, in the impure state, are soluble in amylic alcohol, chloroform, and benzine, whilst in the pure state these solvents do not affect or take them up. What is then required in proving a ptomaine is to ascertain whether such bases lose their primary solubility in the process of putrefaction. It remains to be seen whether this character is exceptional or absolute. However this may be, the Italian Ptomaine Commission creditably attacked a problem which another similar effort may perhaps successfully accomplish.

Profiting by criteria physiological action may

afford, there is the fact that Lieberman and other toxicologists have in several instances obtained from dead bodies an alkaloid closely allied both in constitution and properties with conicine; that ptomaine, however, differs in two respects so markedly as to show an absolute distinction: it is neither volatile nor venomous. During the examination of the body just alluded to, which had been eighteen months in the water, Brouardel and Boutmy met with an alkaloid, blueing test paper, precipitating with Meyer's test, giving with potash a flocculent precipitate, a violet colour with nitric acid at 60°. That alkaloid at first might have readily been confounded with morphine, cadine, brucine, atropine, or veratrine. The similarity to that latter base continued to accompany it through a certain number of reactions. A melange of sulphuric acid and binoxyde of baryum turned the ptomaine to a brick-red colour when cold, to violet when hot, hydrochloric acid concentrated, and boiling developed a cherry hue. Like the preceding tests the physiological effects of the ptomaine seemed to belong especially to veratrine; but whilst the vegeto-veratrine does not reduce the ferricyanide, the cadaveric base of the drowned subject gave immediately the prussian blue in the presence of the ferricyanide and perchloride of iron.

This instance might suffice to show the liability to serious errors, when those intrusted with an examination are either ignorant of the subject of ptomaines or fail to duly exercise the means of distinguishing the vegeto-alkaloid, where every care is requisite in conclusions so delicate and grave.

M. Hugounenq holds that an observation so decisive confirms the possibility of distinguishing, even in examinations the most difficult, a vegetable alkaloid introduced into the system during life from the ptomaine cadaveric alkaloids developed after death ; that by submitting the alkaloid extracts to all the tests which differentiate them it is possible to succeed in distinguishing the one from the other those products which were liable to be confounded before the labours of Gautier, Etard and Brieger fixed the ptomaines in the organic series with well-defined chemical characters.

The Vital Alkaloids

OR

Leucomaines.

PART II.

It is sometimes less difficult to make a discovery than it is to comprehend its significance or what it naturally leads on to. Before the publication of Armand Gautier's remarkable *mémoire*, based on researches and deductions the most complete, evidences as to the existence of a suspected function in animal physiology were not wanting had they been read aright. Singularly enough, no attempt was made to read them. Though alkaline bases had been detected in animal tissues, no one had summarized the discoveries, or thought of generalizing results. But this could not continue, and to Armand Gautier is due the merit of overthrowing the artificial barriers, which theoretic preconceptions had hitherto recognised as separating the physiological phenomena of the animal and vegetable kingdoms, and in attributing exclusively to the tissues of the latter, the power of elaborating alkaloids.

This capacity of the economy in this function

was not even suspected. Liebig and Pettenkofer had long made known the existence of kreatinine in urines; this was the first body of animal origin acknowledged as possessing properties clearly alkaloid. It was known that kreatine detected in animal tissues along with kreatinine resulted from that latter substance dishydrating in contact with salts, acids, or heat; but its presence and production was thought to be explicable by the processes involved. As for the kreatine itself, Liebig declared that it did not possess any of the properties which characterised organic bases. Such was the influence of false theory on minds the least prejudiced. Then, as largely still, it was taken for granted that animal organisms supplied no other nitrogenous substances than those of the nature of amides, unless it were methylamine and trimethylamine.

It was not till twenty years later Liebreich detected the presence of the already known vegetable alkaloid betaine in normal urine. And it is only so recently as 1880 that Pouchet, as the result of long-continued and careful examination of the human urine announced, besides the presence of allantoine, since regarded by Meyer as a uride, karnine and an alkaloid in well-defined chlorate crystals. An-

alyses were incomplete, but the following year Gautier confirmed the fact, that Pouchet's alkaloid possessed the general properties of a ptomaine, and thus was indirectly led to the study of this new class of alkaloids, the product physiologically of animals during life. This preliminary advance was strengthened by Bouchard in 1882, when he disclosed the fact, that not only were alkaloids present in appreciable quantity in normal urines, but that they augmented notably in the course of certain maladies, in typhoid fever for instance. Lepine and Guérin have since found that this applies to a still wider pathological area. Again, Lepine and Aubert, generalising facts acquired, concluded that in the course of certain maladies these poisonous products of the urinary secretion notably increase in quantity until the crisis is reached, when they finally diminish.

To return to 1880, Gautier having satisfied himself that the urinary alkaloid obtained by Pouchet really belonged to the order of ptomaines, directed his investigations with a view to ascertain whether the normal secretions, of certain animals, notoriously toxic, might not owe their activity to substances of a similar nature and origin. By carefully operating on the glands of snakes, he was enabled to elimi-

nate materials unquestionably of the alkaloid order. From the *naja tripudians*—cobra di capello—in particular, two new substances were obtained by him, and evidently of the nature of ptomaines. From the salivas of the reptilia to that of man was but a step. In the same year Gautier, subjecting this human secretion to examination, succeeded in isolating various toxic elements in sufficient quantity to note its action. Though the products in both instances responded to the reagents of Meyer and Nessler, and induced characteristic physiological effects on the nervous and digestive systems of smaller animals and birds, it is more than doubtful if they constitute the direful element of salivary venoms.

But these were not the first essays in this direction. As early as 1852, Cloez, from examination in both reptiles and batrachians, had made known similar results, which Zalesky afterwards confirmed ; in 1874, Meisher and Picard were even so successful, with one alkaloid at least, as to give us both its formula and name —Protomaine.

Facts such as these ought to have impressed inquiring minds, but prevailing views did not permit it. The presence of alkaloids in the secretions was either doubted or allowed to pass

unheeded. Gautier, as we have seen, was not disposed to halt. That eminent professor felt convinced of the pharmaceutic powers of the animal organism in the elaboration of alkaloids, and clearly set forth his views in a *mémoire* published in 1881, whilst later investigation, consisting in exhaustive examination of the muscular tissues, enabled him to give definite confirmation to these preliminary observations. But, before examining his brilliant results, the labours of others who had been similarly engaged require some notice.

A little before the death of Selmi, about 1879, two other Italian investigators—Paterno and Spica, advanced an objection to the effect, that all or a part of the alkaloids derivable from putrefactive materials might possibly have existed during life. In order to decide the point, blood, white of egg, and bread were severally examined, but by inefficient methods; though alkaloidal traces were detected, no analyses were given. Their labours were taken up by the Italian Ptomaine Commission, and with more success. The conclusion arrived at was, that alkaloid substance, obtainable from animal tissues, was neurine resulting from the decomposition of lecithine; that it increased in amount according as either

body is more abundant. "Is that neurine always accompanied with another alkaloid which reagents separate with difficulty?" was a question which they left unsolved; the small quantity, however, deprived it of any toxological importance.

It ought to be noted that the preceding authors had neglected the extractive matters of normal muscular flesh formerly examined by Liebig. In 1883, Professors Guareschi and Mosso resumed its study from the special point of view which now engages our attention. In their interesting work, these last authors state they had obtained directly from veal methylhydantoine, a body apparently of the uride family, and intermediary between the kreatinine, sarkine, and urea; but that they had not found alkaloids properly so called.

Such was the conclusion reached in one of the most conscientious memoirs, which had been published with a view to the elucidation of this question of the production, and presence or absence, of alkaloids in the living animal tissues. It now remains to note, not the preliminary experimental efforts and hypotheses suggested by Armand Gautier in 1881, but the positive results which this eminent investigator has arrived at by a course of continuous

examination and study since that date. The results are most important, as they enable him to affirm to-day positively, that the important chemical function of all the animal tissues, however much it may have been ignored, is the incessant elaboration of alkaloidal products formed at the expense of proteid materials, precisely as urea and carbonic acid are similarly and simultaneously formed. Seeing their albumenoid origin—and in order to distinguish this new class from that of the cadaveric alkaloids or ptomaines (πτῶμα)—Armand Gautier has conferred on those vital alkaloids, the name of *leucomaines* (λεύκωμα), a term he limits to all those alkaloids derivable from albumenoid substances which appear in the animal tissues during life.

I.

Classification and Definitions.

In classifying those alkaloids which arise in the animal economy during life, and which is now methodically practicable, it will be necessary to indicate more distinctly those bases which, if misunderstood, were at least already known.

As has been observed, kreatinine, one of the most energetic of the bases, had long been discovered by Liebig as resulting from the action of hydrochloric acid on kreatine. Vallenciennes and Fermy had met with it in the muscular tissues of crustaceans, finally Pettenkoffer has detected it in urines. It was so far back as 1819 that Marcet, while examining dead bodies, detected xanthine; he also succeeded in isolating it, and even accomplishing its synthesis. Sarkine or hypoxanthine, so widely distributed in the organic world, both animal and vegetable, had also been met with in the principal organs of the economy, such as the brain, liver, kidneys, &c., it is also now found present in

albumenoid putrifying products ; Schuzenberger even finds it in yeast waters. Guanine, discovered by Unger in 1844, has been met with in a great many products of animal nature ; in the flesh organs and excrementitious matter of mammifers, fowl and fish. Virchow had indicated its presence in the cartilages of arthritic pigs ; and quite recently Schultz and Bosshard have detected guanine in association with sarkine and allantoine in the young sprouts of the plane tree, vine, and other plants. To Weidel we were indebted for karnine. This base he isolated from American imported meat, and which he ascertained might be generally estimated to contain about one per cent. Schutzenberger found the base also in yeast waters. Finally in chronological order comes betaine, discovered by Scheibler in beet root (1866) and which Leibrich in 1869 detected in urines, and he has since made known its synthesis.

These widespread products of animal and vegetable organisms, though the feeblest of all the physiological alkaloid series in their alkalinity, are none the less perfectly characterised. Notwithstanding this, as has been pointed out, they attracted but little notice until Pouchet in his remarkable thesis announced the fact of his having succeeded in isolating from human urine

a base which he had carefully examined in its double chlorides of gold, platinum and mercury, and had tested with the ordinary alkaloid reagents. The subsequent researches of Armand Gautier not only completed the series of alkaloids of animal origin now known, but brought the whole into a state for their natural and systematic arrangement. It is in accordance with the most recent light thus thrown upon the subject that we are now enabled to enter on their study under the general name of Leucomaines.

These bodies form two groups—the betaine or uric and the kreatinic. To these must be added that other group—the non-seriate—which goes on rapidly increasing. As the nature and definition of its contents become decided, they will find their exact position in the above orders.

Betaines—Uric Leucomaine Group.

BETAINE $C^5H^{11}NO^2 = \begin{array}{l} (CH^3)^3{=}N - O \\ \qquad\quad\;\, | \qquad\; | \\ \qquad\quad CH^2{-}CO \end{array}$

anhydride constituent of trimethyl-glycolaminic acid. The base, $C^5H^{11}NO^2$, is obtained by adding slight excess of acetate of lead with water; the precipitate, separated by filtering, is decomposed by diluted sulphuric acid. The

acid solution gives, with phosophate-ungestic, a precipitate which easily decomposes with milk of lime. The bases are then separated in the ordinary way.

The synthetic processes of extraction are the more interesting, as also the more practical. These consist in oxydizing neurine with permanganate of potash, or by the action of iodide of methyl on glycol. Betaine, $C^5H^{11}NO^2+H^2O$, forms in abundant brilliant deliquescent crystals. It unites with acids, as also with chlorides of gold and zinc. The chloride of platinum gives with chlorohydrate of betaine a platinichloride in yellow crystals.

KARNINE $C^7H^8N^4O^3$.—With this base the natural series of the uric group of alkaloids begins. It is obtained by precipitating a watery solution of meat extract with baryta, filtering, and again precipitating with acetate of lead. Exhausting the washed precipitate with boiling water, dissolves the plumbic karnine, from which the karnine can easily be removed by sulphuretted hydrogen. If the base is not sufficiently pure, it may be converted into a silver compound and re-treated with sulphuretted hydrogen.

This base is in white crystals, which are little soluble in water, insoluble in alcohol; reaction neutral. It contains a molecule of water of

crystallization ; with the soluble salts of lead and silver, it forms metallic compounds ; it furnishes with hydrochloric acid, salts which the chloride of platinum converts into a crystalline chloroplatinate of yellow colour. Karnine then comports itself closely as a body of the uric group, in which it merely differs from xanthine by the elements of acetic acid.

Treated with watery solution of bromine, karnine yields the anhydride carbonic ; bromide of methyl and bromohydrate of hypoxanthine.

$$C^7H^8N^4O^3 + Br^2 = C^5H^4N^4O.HBr + CH^3Br + CO^2.$$

ADENINE $C^5H^5N^5$.—This base opens the series of the leucomaines of the uric group, properly so called ; has been made known to us so late as 1886. For the purpose of isolating it, Kossel, the discoverer, adopts the following process :—Hashed bullock pancreas is boiled for two or three hours in water acidulated 0.5 per 1000 with sulphuric acid, neutralized with baryta solution, and filtered. The liquor is precipitated with a solution of the ammoniated nitrate of silver. The precipitate, dried on porous plates, is afterwards treated with nitric acid in presence of a little urea. It is then heated in a water-bath and filtered. The adenine is then deposited in the form of double

salts of silver. Along with hypoxanthine and guanine, the precipitate is decomposed with sulphuretted hydrogen. The addition of a slight excess of ammonia to the filtered liquor, throws down the guanine and the greater part of the adenine, leaving the sarkine and traces of adenine in solution. The mixed precipitate is taken up by diluted hydrochloric acid hot. When the liquor cools there is obtained first a deposit of hydrochloride of guanine; by subsequent evaporation the chlorohydrate of adenine crystallizes, ammonia then permits of the removal of the adenine, which may be purified in the state of sulphate and recovered by ammonia.

Adenine, $C^5H^3N^5 3H^2O$, is in large transparent crystals, contains three molecules of water of crystallization. It is very little soluble in cold, but soluble in hot water; insoluble in alcohol, ether, and chloroform; acids and bases on the contrary dissolve it very readily; more soluble in ammonia than guanine, but less so than hypoxanthine.

In alkalinity adenine is neutral; it sublimates at 278° C., emitting an odour of prussic acid; it unites with acids, yielding beautifully crystallized salts. It also combines with a number of saline compounds; with the chloride of pla-

tinum it furnishes a chloroid platinate in yellow crystals.

Potassium acting on adenine at 200° C. gives cyanide of potassium.

$$C^5H^5N^5+5KOH=5CNK5H^2O$$

Nitrous acid converts adenine into sarkine.

GUANINE $C^5H^5N^5O$.—This base is in general obtained from guano, by exhausting that substance with a milk of lime at ebullition ; filtering, then treating the residuum with solution of carbonate of soda ; adding to the acetate of sodium and hydrochloric acid precipitates a melange of guanine and uric acid. Boiling hydrochloric acid converts the guanine into soluble chlorohydrate from which the guanine can be separated with ammonia.

Guanine is a white amorphous powder of slight solubility ; acids and ammonia, however, dissolve it, and this feature differentiates it from xanthine and sarkine.

The oxydizing action of chloride of potash and hydrochloric acid, converts guanine into guanidine and parabanic acid, with disengagement of anhydride carbonic.

With nitrous acid guanine $C^5H^4N^4O(NH)$ is converted into xanthine $C^5H^4N^4O(O)$.

With the bases guanine give compounds ; it unites with salts ; its sulphates, nitrates, chloro-hydrates are known. Picric acid and the chloride of platinum combine with guanine ; with the latter reagent it gives an orange yellow crystalline precipitate, presenting the formula $C^5H^5N^5O.HCl.PtCl^4+2H^2O$, the chloromercurate presents $(C^5H^5N^5O, HCl^2)$, $^2HgCl^2+H^2O$.

SARKINE OR HYPOXANTHINE $C^5H^4N^4O$.—This base is usually obtained from the mother liquor of kreatine by first separating a small quantity of xanthine with the acetate of lead and ammonia, filtering and precipitating the filtered liquid with acetate of copper. The cupric compound is dissolved in boiling nitric acid, and the sarkine precipitated with nitrate of silver which is accompanied with a combination, but soluble, from which the silver is separated by sulphuretted hydrogen.

Hypoxanthine is a white powder somewhat crystalline. It is soluble in 300 parts of cold water, almost insoluble in alcohol. Distilled to dryness, alone or in contact with potassium, it gives cyanhydric acid, a reaction it will be well to remember, as it enables us to ascertain the constitution of sarkine.

The base united with alkalies form with acids

crystalline salts ; acetate of copper and nitrate of silver unite with it. In hydrochloric solution it is precipitated with chloride of platinum ; in the presence of nitric acid by phosphomolybdic acid, it gives the ordinary alkaline reactions. The sub-acetate of lead does not precipitate it.

XANTHINE $C^5 H^4 N^4 O^2$.—Neubauer obtained this base from urine by adding baryta water and the nitrate of baryta which precipitates the sulphuric and phosphoric acids ; the liquor is then filtered and evaporates to a syrupy consistence and precipitates with the ammoniated nitrate of silver. Precipitate is decomposed with sulphuretted hydrogen in presence of hydrochloric acid, the xanthine may then be obtained to the form of a hydrochlorate.

Xanthine may be extracted from muscular tissues in the same way as the sarkine. The two bases are separated by the acetate of lead which precipitates the xanthine, leaving the sarkine in solution. When the primary material contains much xanthine, urinary calculi for example, we can readily dissolve with potash, and precipitate the pure base with carbonic acid, but occasion rarely offers for the use of this ready method.

By whatever process this base is obtained, it assumes the form of an amorphous powder con-

sisting of minute adhesive pellets. According as we rise to the series of this leucomaine group, their solubility diminishes ; the solubility of xanthine is one gramme to 14,500 of cold water, at boiling point 1,156. It is more soluble in acids and alkalies.

Heat destroys xanthine in forming ammonio-cyanide, the resulting hydrogen reduces it to the state of hypoxanthine. It combines with the alkalies, with ammonia in particular, forming xanthates. Acids unite with it to form salts—a certain number of compounds precipitate it : chloride of platinum gives a yellow crystallized chloroplatinate ; chloride of mercury and nitrate act similarly.

Of all the reactions the most important is that with the acetate of copper. It separates xanthine at boiling point only, a character which Gautier, Schutzenberger, and Destrem have frequently utilised in the extraction of that base from the melange in which it may have arisen.

PSEUDOXANTHINE $C^4H^5N^5O$.—This base was discovered by Gautier, and is obtained from animal muscular tissues by the same process as the other physiological alkaloids which he added to the series and which will be described with the kreatinic group.

Pseudoxanthine is a yellow-coloured powder, sparingly soluble in water, soluble in alkalies and hydrochloric acid; with the acid it gives a chlorohydrate, which resembles that of the hypoxanthine. It forms star-shaped crystals, and much resembling those of uric acid. The ammoniacal acetate of lead, corrosive sublimate, and nitrate of silver precipitate pseudoxanthine, as well as xanthine, like the latter pseudoxanthine, gives the reaction of the murexide.

Between the two leucomaines there is consequently a close affinity. Gautier not having met with xanthine in the course of his researches, Hugounenq thinks the substance noted in different parts of the organism, and described under the name of xanthine, was often merely pseudoxanthine; the strong resemblance of the physical properties of the two bases favour the confusion.

II.

Classification and Definitions.

GAUTIER in 1881 having distinctly raised the question, whether in the normal state animal tissues, like the organs of plants, might not be capable of elaborating alkaloids, determined to decide it. The existing bases just enumerated, the analogy of biological phenomena and putrefactive reactions and the production of ptomaines in the course of bacterial fermentation of proteid materials, led him to that series of investigations which were so brilliant in results. They not only confirmed his theoretical conceptions, but established demonstratively the formation of leucomaines by the normal cellular activities of all living things, animal as well as vegetable.

In working out this problem he occupied himself with the study of the alkaloidal products of muscular tissues, because they were abundant, and the nature of the material homogeneous. The new alkaloids discovered by him

are consequently all of fresh meat origin. His researches were conducted with great difficulty but with the greatest care, so as to avoid all suspicion that the alkaloid basic products could have been formed artificially in the course of operations.

According to the method adopted, and laid down for others to follow, fresh hashed meat is first subjected to digestion for twenty-four hours in double its weight of tepid water, to which has been added 0 gr. 25 of oxalic acid and oxygenated water 2 cc. per litre, to prevent fermentation. The residue is filtered by pressure, and the united strainings are subjected to boiling or evaporation, in order to coagulate albumen. The albumen is separated by filtration and evaporated at a temperature of 50° C., and the tissue-residue is then retreated with alcohol at 99°; this, when evaporated, gives a new residue which is further treated with alcohol at 99° this time hot. The liquid having been set aside for some time, ether at 65° is added until precipitation ceases. Examined after twenty-four hours the liquor presents a yellowish thick appearance, and is of a bitter taste. Very soon—but hastened by the use of pure ether—a magma of crystals is deposited, which may be separated. These primary crystals are washed

in cold alcohol of 99°; this removes from them without dissolving them, their impregnating liquors.

Boiling alcohol of 95° relieves these crystals first, of a base described as xanthocreatinine; and, secondly, of crystals which are deposited in the mother liquors of the first alkaloid, which are examined successively.

The primary crystals—free from precedent compounds, and washed with alcohol, leave a residue which is taken up with boiling water. From this aqueous solution is deposited first a primary base—amphicreatinine, and by further concentration of the mother liquors a second —crusocreatinine.

The alcoholic solutions, from which these three earliest bases have been obtained, on being properly treated with acetate of copper, and the precipitate decomposed with sulphuretted hydrogen, gives a new alkaloid which has been already classified as pseudoxanthine.

Thus, in isolating all these alkaloid crystals, the analytical process is speedy and simple. There is no need of any other reagents than alcohol, ether and water. These crystalline substances constitute the new bases, whose pathological, as well as chemical, relations are now exciting so much interest; investigation in this direction has all the prospect of a wide

and fertile field before it. These processes do not exhaust the muscular basic products.

In briefly describing these new compounds, whose discovery is also due to Gautier, it will be necessary to note that long-known base, kreatinine, which heads the list.

Kreatinic Leucomaine Group.

KREATININE $C^4H^7N^3O$ $NH{=}C\begin{array}{l} NH— \quad\quad CO \\ \quad\quad\quad\quad\quad\quad | \\ N(CH^3)—CH^2 \end{array}$

anhydride of guadinine derived from methyl-aminacetic acid.

The method of isolating the base is that of Pettenhofer, modified by Neubauer. 300 cc. of urine is first alkalised with milk of lime. After some hours the whole is filtered and evaporated to dryness by the water bath ; 30 to 40 cc. of alcohol is then added ; a deposit soon appears, which is disposed of by filtration. The mother liquors of concentrated alcohol, to which has been added the chloride of zinc, supplies the well-known combination $(C^4H^7N^3O)^3$,ZnCz whence the kreatinine pure may be easily removed by the aid of the hydrate of lead.

The constitution of this important base is difficult to grasp, and would not only necessitate a review of the synthetic chain of reactions by

which we are enabled to obtain kreatinine, commencing with its elements, but a knowledge of the modes of syntheses of glycocol or amin-acetic acid and cyanide. The method of dealing with these two bodies, and the reactions involved, is not required of us, the object of this present study being rather indicative than synthetic.

Kreatinine forms into clinorhombic prisms soluble in water, slightly soluble in alcohol ; it unites with acids, displaces ammonia in its combination, precipitates nitrate of silver, corrosive sublimate, and gives with the chlorides of zinc or cadmium characteristic crystalline combinations long familiar. Kreatinine gives with acids crystallized salts.

It may be well to note that the facility with which kreatinine yields methylhydantoine and urea, may probably claim for it an important intermediary *rôle* in the physiological genesis of that latter substance, at the expense of the proteid materials.

XANTHOCREATININE $C^5H^{10}N^4O$.—This is the most abundant of these bases, and it closely resembles kreatinine, from which it merely differs by CH^3N. It shows in pellets of sulphur yellow, of slightly cadaveric odour. The base is soluble in cold water, and boiling alcohol of 99° ; reaction strongly alkaline. It unites with

chlorohydric acid. The chlorides of gold, zinc and mercury, give compounds in various crystalline forms ; neither nitric nor oxalic acids precipitate it. The same with the acetate of copper, a character which alone distinguishes that leucomaine from xanthine and hypoxanthine. Of the ordinary alkaline reagents, tannin phosphomolybdate of sodium precipitates the xanthocreatinine.

This base is toxic, and induces somnolence, purgation and vomiting.

CRUSOCREATININE $C^5H^8N^4O$.—This beautiful base differs from the previous one by only two atoms of hydrogen. It possesses the general properties of kreatinine, which it strongly resembles in elements and alkalinity ; differing only by the elements CNH of cyanhydric, and which here again plays a diatomic *rôle*. Crystals are orange yellow, with chlorides of platinum and gold, and give crystalline compounds. This base is neither precipitated by oxalic or nitric acid ; the acetate of copper does not act upon it when heated, consequently it cannot belong to the uric series ; has no affinities with guanidine xanthine, or such like bodies.

AMPHICREATININE $C^9H^{19}N^7O^4$.—Prisms bright pale yellow ; slightly bitter to the taste, little soluble in cold water ; exposed to a temperature

of 110° C. they become opaque in colour without changing their form. The chlorohydrate chlorides and chloroplatinate of amphicreatine are soluble and crystalline. Neither the acetate of copper, nor the chloride of mercury precipitates it. The phosphomolybdate gives a powdery yellow precipitate. It does not give the reaction of the murexide, this consequently excludes it from the leucomaines of the uric group. It has the closest analogy to the kreatinic. Though its crude formula would seem widely to differentiate it, in reality it corresponds to two molecules of kreatine, plus the C N H groupment.

PSEUDOXANTHINE.—This base, whose resemblance to xanthine has led to some confusion, has been sufficiently noticed under the uric group, to which it properly belongs. Nothing more need be said of it.

To terminate the analytical indications of the complete work, in which Gautier has described for the first time the kreatinic leucomaines, it only remains to mention two more complex bases, which are found to accompany the preceding in the muscular tissues. As they have not yet been perfectly studied, we will rest satisfied with giving their formula—$C^{11}H^{24}N^{10}O^{5}$

—$C^{12}H^{25}N^{11}O^{5}$, and their difference from each other by CNH.

The constitution and affinities of these bases with those named would lead to the conclusion that the kreatinic leucomaine group forms a natural series, the terms of which are homologous, as regards CNH ; that is to say, that they differentiate by the cyanhydric arrangement, as the carbonate homologues, for example, differ by the CH^2 groupment. Thus the conception again and again announced by Gautier, of the importance of the CNH unity in the molecule of proteid material, finds here fresh confirmation.

It is, however, well to observe, that the question of constitution is not yet definitely known ; but as Gautier thinks, it would perhaps be as well represented by cyclical nuclei analogous to those of the uric leucomaines, though somewhat modified.

If we recognise the presence of an unbroken circle of chemical affinities linking together the betaine, kreatinine, and the alkaloids of the uric group, we are forced to admit the existence of a cyclical nucleus in the leucomaines best known. This peculiarity may not be altogether accidental. The question, however, need not now be followed farther, as it lies beyond the scope of the present summary.

III.

Non-Seriate Group.

This class comprises those leucomaines which do not come within either of the two preceding orders to which all the well-known leucomaines belong. Being, for the most part, still undefined, any attempt at a rational arrangement would be useless. It is, therefore, best to notice them according to their origin, or that organ or secretion of the animal economy whence they are derived.

When treating of these alkaloids in their pathological and toxical relations, it will be seen how very interesting is the study which they promise—the urinary leucomaines in particular. Their variations in quantity and quality, indicating the condition of health and disease, merit the close attention of competent observers.

According to their sources, we have to note as follows :—

The Urine.—Pouchet's inaugural thesis of

1880 is an important event in alkaloid investigation. It was then that this investigator made known the fact that he had obtained from normal urines a uride, allantoine—a primary base already known—karnine, and a second alkaloid which, as researches have advanced, he has since analysed.

The method of extraction he adopts has already been described, so its principles need only be referred to. It consists in treating the material containing the alkaloids with tannin, decomposing the tannates with hydrate of lead, and submitting the liquors to dialysis. From the dialyzed portion, Pouchet obtained a body in deliquescent fusiform crystals of feeble alkaline reaction, which, when uniting with acid, gave crystalline salts. The chlorohydrate of this base furnished, with the chlorides of gold, platinum and mercury double salts. The analysis of the chloroplatinate lead either to the formula $C^7H^{12}N^4O^2$, or to a formula which merely differs from it by H^2 additional, that is to say, $C^7H^{14}N^4O^2$.

According to Pouchet, urine contains in addition to the above, small quantities of hydropyridic bases, either similar to or identical with those obtained in the putrefaction of fish-substance by Gautier and Etard.

Besides these eminent workers, Villiers, Lepin, Guérin, Bauchard, and others, have been diligently engaged in this field.

Blood and Important Viscera.—Reference has already been made to the joint *mémoire* of Spico and Paterno to the Academy of Lincei, 1882. With a modification of the Stas-Otto method these authorities were enabled to obtain, from bullocks' blood in particular, traces of a substance precipitable with phosphomolybdate, and capable, after a time, of reducing the chlorides of gold and iron. But in consequence of the blood being used in insufficient quantity for carrying out reliable researches of this nature, they were necessarily unable to secure any analysis of such alkaloidal traces as were obtained. The examination of white of egg afforded similar results.

These investigations were resumed by the Italian Ptomaine Commission, whose reports, published in 1885, are interesting to refer to. The Italian chemists, engaged in this enquiry, isolated alkaloid material from the blood, the brain; and from the liver, traces of basic products whose alkaloids were characterisable by their qualitative reactions only. By Stas's method they were enabled to separate from the liver two leucomaines, one in the form of

a sulphate of a violet colour, and capable of reducing ferricyanide ; the second base which gave a crystalline chloride appeared to be neurine. The two alkaloids were determined by general reagents, but without analytical definitions.

Though these investigations were incomplete in many respects, they have not been fruitless. The labours of Guareschi and Mosso have added to the data. Though attaching less importance to the question as a whole, they detected traces of leucomaines in fresh liver, brain, and veal fibre ; this they attributed to the action of reagents or unsoundness of the proteid material, thus ignoring the positive results of their researches. Finally, these authorities found a base, probably neurine, in the fresh heart and lungs. Similar observations have been made by Coppola on the blood of dogs.

The examination of the blood requires to be taken up afresh. This is being done. Aided by the method indicated by Gautier, Wartz has been engaged in investigating the leucomaines in the material drawn fresh from the vein of the animal in order to avoid all possible error arising from impurity of change. By this means, and operating on quantities of fifteen litres at a time, Wartz has obtained crystallized

products of alkaline reaction, which give chlorides of platinum, gold and mercury in well-defined crystals. He has also succeeded in isolating from bullocks' blood volatile bases in the state of chlorohydrates, but in quantities too small to admit of reliable analysis.

The Spleen.—From this organ Morelle, of Lille, has determined the presence of an alkaloid which he has isolated in the form of chlorohydrate in deliquescent crystals and transformable into chlorides of gold and platinum. Labord has now been able to ascertain its physiological effects.

The Intestines. — Pouchet and Villiers have isolated with chloroform, from choleraic dejections, a base which seems to belong to the pyridic group. This substance, which is apparently the product both of physiological digestion and albumenoid bacterial destruction, is highly oxydizable, and energetically reduces the ferrocyanide and chloride of gold and platinum. Its physiological action has also been ascertained.

The Saliva.—The presence of alkaloids in human saliva has been ascertained by Gautier. If the soluble extract of normal saliva is treated with a little ferricyanide, immediately an abundant precipitate of Prussian blue re-

sults. Taking the soluble extract, he treats it with hydrochloric acid and precipitates by Meyer's reagent. This new precipitate being washed is decomposed by sulphuretted hydrogen, which on being filtered gives a solution that by evaporation leaves fine minute hydrochlorate crystals. The effect of the substance on small animals has been attested. We merely indicate the fact, as it will be more fully noticed when treating of the leucomaines in their physiological relations.

The Venoms of Certain Snakes and Batrachians.—Investigations in this direction, if not fruitful, are at least interesting. Following the traces given by Cloez and Gratiolet, who obtained alkaloids from the cutaneous pustules of toads, Zalesky succeeded in isolating from a species of lizard, a base of the formula $C^{34}H^{60}N^{2}O^{5}$; while Gautier, operating on the venom glands of the *Naja tripudians*, has been enabled to separate two more.

Certain Molluscs and Fishes.—Of this class little need be said. The reason of the poisonous effects of certain shell-fish and fish proper is no longer a mystery. Though it is long since Salkowski, Schmidtmann and Virchow drew attention to the subject, it remained for Brieger to identify the active principle in the mytilotoxine and give its formula, $C^{6}H^{15}NO^{2}$.

Such in summary is the list of the chief unclassified leucomaines. Their characters, like those embraced in the preceding groups, will be made more evident when their toxic properties come to be considered. From the nature of our introductory survey of the subject, the physiological actions of the leucomaine animal alkaloids will be more intelligible treated separately and as a whole. In indicating the number of recent researches, or of those still in progress, whilst noting the work of earlier observers, the object of the present paper is accomplished.

IV.

Physiological Actions.

To render the review complete so far as it is at present possible, it will be necessary to consider the toxic and physiological actions of the leucomaines. In this respect their study has not yet acquired the development which it presents in the case of the ptomaines ; particular estimates consequently do not come before us with the definiteness which might be desired. In other words, conclusions cannot be adopted without a certain disregard of investigations, which are incomplete or still in progress.

The discovery of the leucomaine alkaloids is too recent to admit of tabulation as regards their physiological action. It may, however, be safely affirmed, that where they have been obtained in sufficient quantity for experimental purposes, they have in general been found to be deleterious to the animal economy, and this irrespective of the group to which they belong ; that in variety and toxic intensity they are com-

parable with those of the ptomaine or cadaveric alkaloids, as these latter are with those of vegetable origin which supply us with the most active known as yet.

The kreatinic leucomaines, Gautier assures us, are deleterious,—xanthine for example,—in very small traces. They exert a powerful influence on the nervous centres, producing sleepiness, lassitude, or occasionally vomiting and purgation; they operate, in fact, in the manner of the alkaloids derived from venoms, though less actively.

The spleen alkaloid of Morelle, as reported by Labord, may be taken as typical of the toxic bases of the structures, special or general. This observer noted its action as embracing stupor, paralysis of reflexes, convulsions and death. Injected into the cellular tissues of the guinea pig, frog, &c., there is immediate toxic action, followed by collapse, gradual functional subsidence, with death in a few hours. The post mortem appearances may also be regarded as of general application. There is marked and rapid visceral ecchymosis and œdematous infiltration, with cardiac systolic arrest.

Interest obviously increases as we approach the excremental products. The study of the

intestinal and urinary excreta to begin with, notwithstanding all that has been done, shows new and yet more complex aspects of the chemical problem to be dealt with.

The probable double origin of the intestinal leucomaines, for example, does not materially affect that of toxic action. The alkaline base that Pouchet isolated in the form of chloro-hydrate, is unquestionably poisonous, a fact of which this eminent investigator had serious personal experience. It is found sufficiently energetic to control the heart's action, and to induce death, followed rapidly with cadaveric rigidity. This authority has also met with traces of alkaline substances in the cultivation liquid of the comma bacillus of Koch, and which would appear to be identical with the preceding. The more recent examination by Villiers of dejections of choleraic subjects, goes to strengthen this impression.

Whether defined or undefined, as has already been remarked, the urinary leucomaines stand first, in interest and importance, in a physiological sense. It was through the urines that their discovery and investigation was first entered on; it is through them that the presence of the alkaloid in varying traces is being recognised as a valuable index of the state of the

animal economy, so variable in the conditions, of health and disease. Clinically, this must soon come to be admitted. Facts such as these explain the value some would attach to them, and encourage the study rather of their pathological significance than of their chemical definitions, a field where much more caution is requisite.

Though scarcely traceable at times in normal, healthy urine, the alkaloids show, as Gautier has clearly established, their amount to be relatively increased in disease. Lépine and Guérin find that in the course of certain fevers, for instance, their poisonous quality increases in due proportion until the crisis is attained. But their presence is not perceptible in all maladies indiscriminately, nor always in a like degree in those where they are perceptible. The above-named investigators, for example, have detected the presence of alkaloids in the urines of typhoid and pneumonic patients, but not in those diabetic. Again, it has been ascertained experimentally that the basic products vary according to the morbid conditions, not only in their toxic activity but also as regards their chemical characters. On this point we are indebted to Bouchard for his extensive and delicate examination of urines. He has, for

instance, given averages of the alkaline products of given typhoid fever patients within a space of twenty-four hours, and shown that the leucomaines in certain forms of this fever, and under certain morbid conditions, are not so potent as might be supposed ; experimentally, they need not even pass beyond simple dilatation of the pupil and acceleration of the heart's action.

The later researches of Bouchard, however, have led him to think the poisonous symptoms induced are neither altogether nor always attributable to the alkaloid material. The agent of intoxication, and the intoxication itself are, he believes, often affected by influences which are as yet imperfectly represented. Observations on the venous injections of urine tend to confirm the impression, while still more recent investigation would seem to show that the day urine affords a narcotic, sedative principle ; the night urine, on the contrary, is marked by a stimulant, convulsivant principle.

Supposing that we turn from human urines to human salivas. In these, as we have seen, Gautier has also found extractive matters which respond to alkaloid reagents, and which further investigation will show to be

not without analogies with the preceding, should their toxic properties be verified. The extract, obtained from about twenty grammes of pure saliva secreted during the day, when injected into the subcellular tissue of a small bird, produced intense stupor and drowsiness, which lasted for some hours. Bouchard's day urine alkaloid induced the same effects, while that of the night was exciting even to convulsions. It is not impossible, as Hougenenq suggests, that the night salivas of man might exhibit a similar action, and be also convulsive. The observation is worthy of the attention of the physiological experimentalist, as there is a possibility that the toxic principles of the human saliva, if not identical with that of human urine, at least obey the same laws, though widely differing in their elementary natures. As it is unnecessary to discuss the probabilities of the secretion of such antagonistic principles, we merely note the singularity which ascertained facts in some sense suggest. It would certainly be remarkable, if true, to find the alkaloid in the interrupted succession of physiological effects, guaranteeing, as it were, the alternations of sleep and wakefulness.

From man to the inferior animal is but a

step. Passing from the salivas of man to those of the poisonous reptiles, the difficulties of the subject increase, and the greater caution is required in dealing with them. If the venoms of certain snakes, for instance, have long excited scientific interest and attention, it has been more with a view to the controlling of their terrible effects, and the discovery of specific antidotes, than to their chemical nature and constitution. It was not until Armand Gautier undertook his comprehensive investigations in this direction, that the mystery of their nature and action could be in some sense disposed of. By operating on the venom of snakes of India, more particularly the cobra-hooded snake, he has succeeded, as we have seen, in isolating their alkaloidal bases. His partial examination, analytically and physiologically, are but details in the net results of his researches. Starting with the pure secretion, Gautier found that a milligramme induced immediate disturbance of the primary functions, and was followed with convulsions, whilst death exhibited the characteristic systolic arrest with muscular insensibility to electrical stimulation. He further ascertained the fact that the venom, when submitted to a temperature of 120 to 125° C., underwent no

appreciable alteration, thus clearly showing that its active principle could not be of the nature of a diastase. Its toxic action remaining constant when relieved of all its proteid elements, made it further evident that its poisonous property could not be attributable to the presence of alkaloids alone. Perchloride of iron and the essences had no sensible influence on the venom. Tannin, and the nitrate of silver moderated its action, while ammonia and alkaline carbonates produced but little effect. Weak caustic potash arrested the action of the secretion ; while previous alkaline saturation of the material did not revive its toxity. The gastric juice, on the contrary, seemed to increase its activity.

Gautier's researches are by no means exhaustive, but there is little doubt that he is justified in his conclusions, namely, that the toxic action of the snake-venoms is not simple but multiple, due to the presence of various nitrogenous principles, of which the most energetic is not of an alkaloidal nature. He has, however, as already stated, been enabled to isolate two leucomaines, — precipitable with Nessler's reagent and the iodide of potassium,—which give salts and metallic chlorides in well defined crystals, and induce in smaller animals well-marked physiological effects.

The fact is well attested that certain classes of fish possess the power of secreting a toxic principle somewhat similar in physiological properties to the venoms of the ophidians. Those known, are met with chiefly on the Chinese and Australian coasts. Carri and Gautier have given attention to this fact, and the latter is of opinion that the venomous glands secrete alkaloid material as a normal function. The active principle has not yet received sufficient experimental examination—either chemical or physiological—to warrant conclusions on this point.

Poisoning with shell-fish too frequently occurs to escape notice. Here, again, it is only very recently that the probable nature of the poisonous principle has been suspected. That of the common mussel is an example. Brieger has succeeded in isolating from that mollusc its active principle — mytilotoxine. He has even studied and defined its chemical and physiological properties. Its formula is $C^6H^{15}NO^2$; its effects curaraizing or convulsivant on animals, inducing death by accumulation of carbonic acid in the blood, and paralysis of the motor nerves. It thus resembles the impure extracts in its effects. This base is, however, not the only one; Brieger has detected several others, which are less active, or altogether inoffensive.

The same authority also confirms the observation made by Salkowski, relative to the removal of its toxic properties by distillation with carbonate of soda. This supplies a fact in physiology and hygiene, of important practical application, which has not been lost sight of by consumers.

In taking leave of this subject, it is but proper to repeat that though the presence of poisonous alkaloids in the foregoing secretions is not to be questioned, they do not alone explain the whole of the toxic phenomena, and leave us still in doubt as to their import in those cases where, as Gautier has concluded, the activity of other azotized principles preponderate.

The notice of the leucomaine alkaloids is now complete, at least in summary. A number of recent researches still in progress has been reviewed; it has also been endeavoured to make evident the fact,—no longer questioned,—of the presence of alkaloids varying in their nature and action according to the physiological and pathological conditions of the economy itself. Some of the leucomaines, it has been shown, belong to types already known, and thus group themselves in the natural order of organic compounds; while others, again, form a class as yet ill defined and awaiting further examination.

Now come the important questions: What is the origin of the singular products of living animal tissues? What is the mode of elimination of the alkaloids, whose physiological action occasionally reminds us of that of the most violent poisons? What can be the mode or mechanism by which the cellular stroma, in health and disease, accomplishes those gradual and successive simplifications which the albumen undergoes in running the pyridic circle? The solution of the problems involved, were it possible to follow them, would form the most interesting chapter of normal physiology and pathology of cellular life. If a completely satisfactory reply to the above questions may be hoped for, it must be admitted the time has not yet arrived. The genesis and rôle,—the complete history of the leucomaines, in fact,—is too closely bound up with the essentially vital to permit of it. Following on the present lines of investigation where so much has been accomplished, it remains to be seen what that amounts to.

V.

Biochemic Aspects.

Since 1882 investigation has thrown much light on facts in bio-chemics which were little understood, and very disconnected. It would seem, for example, that the common origin of the cadaveric and physiological alkaloids asserts itself with evidence sufficiently clear to justify a consideration of the question. Seeing how much the prevailing pathological and therapeutical notions would lose as well as gain were this confirmed, it is, perhaps, surprising that the attempt should not have been made sooner. Until to-day, however, both data and induction were wanting. How, then, does the matter stand at present?

Life, I presume, may be scientifically regarded as the incessant mutation of organic elements and tissues. The chemical reactions on which it depends give rise to a number of substances allied to different types which form the basis of a natural classification of organic compounds. The formation of essential oils, sugars, acids, and

fatty substances, at the expense of organic economies, had not escaped the observation of the chemists ; but theoretic pre-conceptions and practical difficulties in experiment long prevented them from seeing the presence of alkaloidal products in the tissues of plants to begin with. In 1817 Sertuerner recognised as an alkaline base one of the crystalline compounds—morphine—which he obtained from opium some years earlier —1804. All know the development which the question soon assumed in connection with the discoveries of Pelletier, Caventou, de Robequiet, and others.

If the history of nations repeats itself so does that of science. Some yet living can remember with what hesitation chemists acknowledged the alkaloidal fabricating powers of plants, and all have witnessed a like hesitation in accepting the discovery of the same function in animals. It is true, that prior to recent researches, some alkaline extracts of animal tissues were known. This is not disputed ; but until more recently no one had looked upon the discovery otherwise than as a solitary or isolated fact.

It was in the products of putrefaction of albumenoid material that the alkaloids of animal origin were first discovered by Armand Gautier, in 1872. Much interest this event

excited when some time afterwards Selmi, of Bologna, published his observations confirming the discovery of the French *savant*, in their medico-legal applications. The question, however, in Italy, confined itself to researches in toxicology, whilst in France first, and next in Germany, it took a position more important and wider in its range. When Gautier, Étard, Brieger, and others by their labours gave precision to the data previously acquired, adding largely to the varied and careful examination of cadaveric tissues, they forced upon us the conclusion that, during the putrefaction of nitrogenous animal material, there are formed organic bases, fixed or volatile, presenting, by their chemical and physiological properties, the closest resemblance to the vegetable alkaloids. Such were the results arrived at in the series of researches which form the first stage of the history of the discovery of organic alkalies derivable from the animal economy.

Now, are we to regard this discovery as of a chemical value only, or as merely a conquest, interesting but isolated, of chemical putrefaction? Surely not. The elaboration of alkaloids must not be regarded as depending solely on the presence of micro-organisms which derive their vital nutriment from the destruction of proteid material;

this is a function much more general, one common to all living cells,—belonging as much to the superior animal as to bacterial activities. Thus regarded, the discovery of alkaloids arising in tissues — whether undergoing bacterial destruction, or during their vital physiological growth—appeals to us as a chemical discovery. Very naturally it does this, but much more than this; for it must be regarded as indicating an entirely new function.

Again, the second stage of the history of the detection of alkaloids in the animal economy is associated with the name of Armand Gautier. It is to this *savant* that we are chiefly indebted for the examination separately of alkaloids formed during bacterial destruction of albumenoids, and of those which owe their formation to the chemical activities of normal tissues. This distinction is useful, and lends itself to the requirements of methodical classification. But does it follow that the terms ptomaines and leucomaines should be considered as absolutely distinct; and as it were, opposed to one another? This is not admissible. It is often in vain, to try to trace rigorously where the one series of alkaloids begins or the other terminates.

In studying the death of the tissues, we find it to be a complex phenomenon of long duration,

and to consist of transitions from biological reactions to reactions of the purest chemical nature. This process is carried on through the medium or intervention of organisms with which the two kingdoms—animal and vegetable—are alike identified, and which in destroying the proteid materials leaves as a residuum of its molecule those alkaloids of putrefaction which are studied under the name of ptomaines. This tissue-death is but a prolongation of life, and the rôle of the bacterides does not mask, so much as might be supposed, the chemico-biological reactions of normal tissues. The discovered residuum being now detected in the disassimilations of muscular structures and various organs of the vital economy, we are enabled to confirm the fact that a certain number of alkaloids are common to the ptomaine and leucomaine series. To satisfy ourselves of this we have only to trace backwards the history of xanthine, choline, and some other bases met with in both the physiological and putrefactive products. The double source of these alkaloids clearly shows that it is by virtue of reactions identical, or at least analogous, that they originate in the two cases, and that nothing more nearly resembles the phenomena of life; that is to say, the reactions of proteid materials undergoing destruction, are

strictly analagous to the phenomena of putrefaction which arise out of the destruction of the same materials under the influence of ferment. Must we then recognise an absolute distinction between the alkaloids of animal origin and those of vegetation. Experiments in this direction carefully studied are in formal contradiction with such a view. The physiology even more than the morphology of organisms confirms the adage of Linnæus, so often and fitly cited, *Natura non facit saltus:* and nowhere is this more evident or more easily realised than in the study of comparative biology. Of all plants the mushrooms are those which, in their nature, bear the closest resemblance to the animal organisation. Now, the mushroom alkaloid—muscarine—has been detected in the products of putrefaction of animal tissues. The beetroot, higher in the organic scale than the *agaric*, elaborates betaine, which Liebrich has succeeded in isolating in the human urine; even those leucomaines of the uric group, adenine, guanine, sarkine, regarded until yesterday as peculiar to and characteristic of animal tissues, are today detected by Schultz and Bosshard in the tender shoots of plants. It is true that the ptomaines and leucomaines exhibit simpler chemical formulas than vegetable alkaloids for

the most part do. The constitution of these latter being less known, their synthesis has not been accomplished, whilst a number of the leucomaines can be manufactured artificially.

The physiological action of alkaline bases of animal origin does not present the diversity of action which gives to the study of the vegetable alkaloids so much interest and importance ; still the physiological effects of some ptomaines and leucomaines are powerful enough to bear comparison with those of the muscarine, curara, and some other vegetable poisons. To summarise matters, the differences in detail do not invalidate the very marked resemblance which group all the alkaloids into one large class. For whether they be the product of the organs of plants, or elaborated at the expense of the albumen of animal origin by bacterial action, or the cell-vitality of superior organisms, vegetable alkalies, ptomaines and leucomaines have the same origin, the proteid materials, and are identical in their genesis ; that is, proteid disintegration.

It is, in effect, in the molecules of the albumen that the origin of the alkaloid has to be sought ; it is by processes of molecular simplification that these ptomaines, these leucomaines are formed, every species of which represents a degree in the retrogressive disassimilation of the

primitive compound. We have observed nucleine under the influence of slight acidity giving up the uric compounds, which in their affinities are so closely allied to cyanhydric acid, as Professor Gautier has so ably demonstrated ; and this irrespective of the source of the nucleine and the condition of the cells which supply it. But this proteid breaking up is not always accomplished in the manner here indicated. According to the recent observation of Kossel, the nucleine of the unhatched fecundated egg refuses to split up, and consequently affords neither xanthine, nor hypoxanthine, nor guanine, nor adenine ; the dislocation only takes place by incubation in the hatched egg, in the embryo, and here we touch on one of the most obscure facts of cellular life—fecundation. The action of the spermatozoon upon the egg, however necessary, is not sufficient, it can only operate by favour of incubation. In the same way bacterides at a low temperature may remain in contact with albumen without exciting putrefaction ; in the same way, also, the spermatozoon may be brought in contact with the egg without formation of the embryo resulting. When incubation raises the temperature, embryonic evolution commences, and the nucleine of the cells undergoes a transformation which renders

it capable of dislocating like putrid albumen, and thus of furnishing those uric leucomaines which we have frequently met with.

This is an interesting example of the phenomena of putrefaction, and those of normal life; it is also evidence of the part bacteria play in the genesis of the leucomaines. And how suggestive also of analogies in the physiology of common life is this. Free expiration of carbonic acid, for example, would seem, in a great measure, to correspond to the aerobic life of the tissues; whilst the greater part of the excretive products correspond to their anaerobic life. Is it not after sleep or perfect repose that the economy is more especially anaerobic, and consumes more oxygen than it receives? It might give an interesting turn to physiological investigation if we endeavoured to determine the parts of the organisms of the vertebrata in which the functions aerobic and anaerobic are localised. The rapid march on lines more assured would seem, however, to render this unnecessary. The various facts acquired prove too definitely the uniformly constant formation of alkaloids in the economy of animals to permit us to assign the elaboration of these leucomaines to a particular category of cells. It is well to note that in the case of the

superior animals the preponderant *rôle* of cellular elements in the production of these bases does not prevent bacterial action in certain organs from resulting in ptomaine formation. The excrementitious products are evidence of this. It is, however, as difficult to trace the mode of operation of bacterides, and the cells of the alimentary or digestive canal in the genesis of the intestinal alkaloids, as it is to limit the domain of physiological putrefaction and digestion to that *ensemble* of multiple complex relations which constitute complete digestion.

From this point of view, and without entering into the broad question of pathology, it may be said that the comportment and origin of animal alkaloids have been misunderstood if it be asserted that their properties exclude the play of micro-organisms in the history of maladies; it is pangermic extravagances that are to be condemned. Contagion, incubation, and the benefit of antiseptic precautions secure for bacterial conceptions, when properly understood, the importance they legitimately claim, and which no scientific mind wishes to deny them. The formation in the economy of animal alkaloids by bacterial and cellular processes unquestionably explains the genesis of many maladies. It does not exclude the *rôle* of the infinitely little in the

category of affections admittedly micro-germal, parasitic ; within demonstrable limits it explains and confirms it. In the actual state of science our knowledge of the respective operations of bacterides and leucomaines in the genesis and evolution of disease is necessarily incomplete ; neither the chemistry of the one nor the physiology of the other have yet been fully seized. The leucomaines, however, clearly belong to both provinces, and their discovery, origin, and properties suggest comparison with putrid reaction. Comparative study of this point has enabled Gautier to ascertain the fact that four-fifths of our tissues live aerobically ; and that the remaining fifth part, on the contrary, lives anaerobically, that is, after the fashion of putrid ferment. Certain tissue transformations then present the same cellular action as the anaerobic ferments do. Thus, during life, in health and disease, miasmatic or enthetic, toxic alkaloids are elaborated, as also in putrefaction where life has ceased. Under conditions of imperfect oxidation and physiological combustion, the natural emunctories, the kidneys and the intestinal canal, evert, by elimination, the risks of disturbance to the organism by the poisonous elements of its own production.

Thus, from one extremity of the scale of

living things to the other, biological chemistry presents us with a character of unity the most striking. Bacterides and cells of superior organisation may lead the same existence, and observe the same laws, and leave as a residue of their activity the same principles alike toxic for all. Life, according to Gautier, is not bound by any externally anatomic form, much less by the cell and its granules. Life is the consequence and the resultant of the mode of aggregation, and the mechanical and chemical properties of plasmic materials and their formal parts. They perpetuate and undergo modification by continuity in transformation of the molecular conditions and the physico-chemical phenomena which take place in these aggregations developed under the influence of similar aggregations pre-existent.

TABLE.

The following is a list of the principal Animal Alkaloids, which have been submitted to ultimate analysis, arranged according to the classification observed in the foregoing pages:—

PTOMAINES
OF CADAVERIC OR PUTREFACTIVE ORIGIN.

I. Non-oxygenous.

Parvoline, $C^9 H^{13}N$
Hydro-collidine, $C^8 H^{13}N$
Collidine, $C^8 H^{11}N$
Neuridine, $C^5 H^{14}N^2$
Cadaverine, $C^5 H^{16}N^2$
Putresceine, $C^4 H^{12}N^2$
Mydaline

II. Oxygenous.

Neurine, $C^5 H^{12}NO$
Choline, $C^5 H^{15}NO^2$
Muscarine, $C^5 H^{15}NO^2$
Gadinine, $C^7 H^{16}NO^2$

LEUCOMAINES
OF VITAL OR PHYSIOLOGICAL ORIGIN.

I. Uric Group.

Betaine, $C^5 H^{11}NO^2$
Carnine, $C^7 H^8 N^4 O^3$
Adenine, $C^5 H^5 N^3$
Guanine, $C^5 H^5 N^5 O$
Sarkine, or Hypoxanthine, $C^5 H^4 N^4 O$
Xanthine, $C^5 H^4 N^4 O^2$
Pseudo-xanthine, $C^4 H^5 N^5 O$

II. Kreatinic Group.

Kreatinine, $C^4 H^7 N^3 O$
Xantho-creatinine, $C^5 H^{10}N^4 O$
Cruso-creatinine, $C^5 H^8 N^4 O$
Amphi-creatinine, $C^9 H^{19}N^7 O^4$

The Physiological Alkaloids

OR

Leucomaines

In Relation to Scientific Medicine.

PART III.

Gautier, whose name stands first in connection with the discovery and investigation of the vital alkaloids, has had the courage to approach some problems of physiology and pathology, the most abstruse and complex in their nature. His recent *memoire*, which abounds in startling inductions, opens up a wide territory that has hitherto escaped investigation. If the indications he submits meet with the attention they deserve, a sweeping reformation may be looked for in our modern medicine. His method of dealing with the questions they involve reminds us little of pangermic and bacterial theorisings ; he takes his stand on data which are positive, precise, and easy of verification. Organic chemistry being a science which is eminently exact, investigating minds may therefore very profitably bestow on it a share of the attention

they have hitherto directed so exclusively to bacterial and bacillar biologies. In any case, what is most devoutly to be wished, is, that efforts will be made to find how the two theories, apparently opposed to each other, actually harmonise, and how they mutually complete and complement one another.

In bringing to the aid of the medicine of the present, the medicine of the past, Peter has also rendered signal services to science. Though the grand time-honoured doctrine has of late lain somewhat in eclipse, he, like many others, knows full well that, from him of ancient Cos to Sir John Forbes, traditional medicine supplies the only glimpse of truth to be met with in Hygeia's dimly-lighted corridors. No one should blink the fact that antiquated humoralism is still a fundamental principle of the healing art, though some have not been told so, and others have forgotten it. Those who are aware of this, and feel ashamed to own it, are to be pitied. As for the judicious who have been dreading recent doctrinal caprices, they may feel perfectly assured that when the prevailing etiological mania loses its intensity or subsides, it will be found to have been much less revolutionary than was generally supposed.

Since Selmi first called the attention of toxicologists to the existence of cadaveric alkaloids, and Gautier ascertained more definitely their characters, the questions they involve have been very much advanced by them and others, Brouardel and Boutmy in particular. Besides proving the fact that animal tissues in process of putrefaction and decomposition invariably elaborate certain alkaloids of powerful toxetic properties, they and others have had reason to suspect that substances of a poisonous nature are variably elaborated in animal tissues, even during life ; and that through the medium of tissue-transformations, or independently and alone, their action is sufficient to determine specified maladies and death. Thus the exciting and proximate cause of the conditions of those under clinical observation promises to become more accessible and available to the practitioner in a numerous class of cases. These suspicions they have to some extent verified. In their hands, analysis of the various secretions and excretions of patients representing a variety of morbid conditions, has led to the detection of substances closely resembling, if not identical with, the alkaloids of putrefaction. Subjects suffering from rheumatic tetanus, progressive paralysis, and progressive imbecility,

for example, yielded bases allied to aconitine and conia; the first, experimentally observed, showed a specific action on the nervous centres, destroying their activity, diminishing general sensibility, the respiration, and the action of the heart.

But such suggestive data, in part acquired, in part foreseen by others, demanded closer sifting and more reliable adjustment, in order to make clear their scientific purport. To Gautier, the eminent French chemist, is entirely due the credit of reducing them to a consistent whole, and thus presenting their practical significance in theoretic form. He confirms the fact that not only after death, but even during life, the animal organism, in accordance with physiological chemical processes easy to determine, has the power of elaborating a numerous class of alkaloids; that these alkaloids —which he calls leucomaines—are essentially toxic in their properties and actions on the economy that gives rise to them; that an auto-intoxication characterised by hyperthermia, hypothermia and allied morbid phenomena indicate the process of their physiological action. Some, with all the force of preconceived ideas, may naturally exclaim, "Well, admitting this to be true, what is to become of the bacterial impedimenta with which we have been harnessed?

These alkaloids we have never heard of!" Well, we can only reply, that the circumstance is much to be regretted; that their existence is by no means a thing of yesterday; some workers have been familiar both with them and with their probable action for years. But in any case, it is never too late to learn; and to begin with, all must know that we are busy chemically manufacturing alkaloids every instant of our lives. As the organism can form alkalies, ammonia for example—seeing how marvellous are its pharmaceutical potentialities—why should it surprise us to find it forming alkaloids? It is only a question of chemical degree. And this most certainly it does, whether the fact we are contending for be accepted or rejected.

This function may certainly be a dangerous one, and might oftener prove fatal than it will be found to do, were it not that the action of its products are ingeniously frustrated and they themselves got rid of in one way or another. Their deleterious manufacture is, in reality, an essential element of life itself. Life is a contingent phenomenon, consisting of a series of partial births and partial deaths. It has been said, and truly said, "in the midst of life we are in death;" for, scientifically speaking, it must be admitted that the living body always

bears with it the components of the dead one. If the organism is to survive, the organic and the inorganic must march hand-in-hand till death severs them.

It is principles such as these, whether understood or not, that sound traditional medicine has always recognised. What Gautier has been showing, and shows so admirably, is simply that the school of the past and the school of the future will be found to mutually support each other, and further, that humoralism, if you will, so far from being vanquished, has been only stolidly refurbishing its arms and reinspecting its resources; whilst pangermism has been exhausting its energies in sensational demonstrations of bacterial surprises and bacillar blunderings.

The still more recent *memoire* of Peter ought to make this evident to those who are unshackled and capable of thinking for themselves. In a passage as remarkable for frank originality as for sound scientific force, he treats us to retrospective glimpses from personal experience, and admirably illustrates the type of mind of those who profit by the current of the day while swimming with it.

The import of authoritative teachings such as these has neither escaped the attention of the

germ theorists on the one hand, nor of the advocates of the unity of poisons on the other. In Germany the intoxication of the system by substances which are the product of abnormal physiological processes has received the name of Botulism. The classes of cases towards which the observation of clinicists has chiefly been directed hitherto are those exhibiting the symptoms and conditions which Asiatic cholera presents. The patients so affected have all the appearance of toxication, and by the poisonous alkaloids—that is, the vital alkaloids or leucomaines. The symptoms which usher in the seizure indicate a form of poisoning so obviously that the chiefs of the bacillar theory of cholera — Koch to begin with — have been compelled to hesitate and ask themselves whether, after all, some ptomaine or other may not be the specific cause of the choleraic mischief, while claiming for it a bacillar origin. Klein, it would appear, is clearly of this view.

Peter has submitted similar facts observed, in order to point out more fully the purely physiological method by which Gautier deals with the problem, which for medicine is of such etiological importance. Gautier, in fact, has clearly shown that four-fifths of our dis-

assimilations are the result of internal economic combustion, and that the remaining fifth is produced at the expense of the tissues themselves. This, in a certain sense, leads us back in the direction of would-be discarded humoralism, because poisoning by a soluble alkaloid is poisoning by blood which has already undergone decided deterioration.

We instance cholera as the aptest illustration of this view. Monopolising, as it does, so much scientific interest, it supplies the freest field for airing the respective claims of two pathological theories which for the moment are apparently in mutual opposition. The one bacillar, organic and strictly biological; the other toxic, inorganic, and strictly biochemical. The first, so high in favour, and with the entire field to itself, has failed egregiously in its assumed solution. The various expeditions—Indian, African, and European—undertaken in bacterio-bacillar interests, have proved as practically hopeless and unprofitable as the discovery of a north-east passage to Cathay. By such missions Koch has only added to his hypothetical perplexities, while Klein, with modified appreciations, preserves his germ proclivities, and hopes by veiled, but truly humoralistic concessions, to solve the cholera problem among others.

Taking their stand on the natural history of disease and physiological chemistry, neither Peter nor Gautier are given to speculation. The first observes the course of maladies and the nature of their products. The second demonstrates the bio-chemical data with which they are intimately associated, and only with a prudent caution looks beyond them. The recently discovered ptomaine alkaloids have given us the measure of nature's pharmaceutical potentialities in death ; Gautier, in directing our attention to the more recently discovered leucomaine alkaloids, has given us the measure of the same potentialities during life ; he demonstrates their toxic properties and the means by which the living organism escapes their deleterious action, and shows that they will be found to constitute *materies morbi* as various as the conditions with which they are associated, and that they are the cause of some of the most serious accidents to health that medicine has to fight against or man is liable to suffer from.

The objects of these comments must now be evident. It is merely to advance those claims which the views of Peter and Gautier, with reference to the causes and nature of disease, have on our acceptance. Our contrasting such claims with those of the advocates of the bac-

terial theories now dominant, may, as a natural result, cause alarm, if not amusement, in many quarters. But those who know that diseases are not entities but processes, concern themselves but little with time-serving theories; they are well aware that even where they do perhaps contain a grain of truth, they still form but a part and not the whole in that broad conception of pathology which is at the same moment ever old and ever new.

Seeing the interest which Gautier's work is likely to give rise to, and how much it is calculated to correct and mitigate the excesses, both in the theory and practice of germ pathology, still in the ascendant, we will now proceed to briefly summarise the work on which Gautier has been so long and arduously engaged, and which promises so much of what our—so-called scientific—medicine stands in very sad need of.

I.

Physiological and Pathological Significance.

Generalising his researches, Gautier announced, in 1885, that with the excretions of healthy living animals there were substances of the nature of ptomaines almost uniformly present. He showed that the alkaloids of the urine of Leibrecht and Pouchet ought to be classified with the putrefactive alkaloids then known; he detected similar alkaloids in the muscular tissues and saliva. To these he gave the name of leucomaines, in order to distinguish them from ptomaines or cadaveric alkaloids. In another *mémoire*, which he has published since, he pointed out what appeared to him the important relation which these products bore to the genesis of maladies, when their elimination by the kidneys, liver, skin, and intestinal mucous membrane was defective or suppressed.

With a view to confirming these preliminary observations, he took up the study of the sub-

ject, carefully examining the muscular juices of the larger animals. He succeeded in adding to the list five new alkaloids, all perfectly defined, crystallised, and having a specific action on the nervous centres, more or less marked; inducing somnolence, lassitude, some of them even exciting vomiting and purgation—effects similar to those of poisonous alkaloids, but less active than the cadaveric alkaloids. He satisfied himself of the fact that these bases originate during life as naturally and legitimately as carbonic acid and urea. It only now remained for him to ascertain by what mechanism, or process, those alkaloids originate and assume their definite forms and characters; how they comport themselves in the physiological, pathological, or putrefactive, correlations; what follows from their incessant formation in the economy; what becomes of them, and finally, how the organism itself escapes their deleterious effects. In common with previous and contemporary scientists, he found the lines of the enquiry vague and disconnected. Here want of space forbids our following him; we push on to his conclusions, and nothing in induction can be clearer.

While profiting by physiological facts acquired, and the knowledge that the oxygen of the atmosphere, by means of the respiration

and the circulation of the blood, finds everywhere its way throughout the animal organism, he cannot admit, as is generally assumed, that animal life—in other words, the successive phenomena of assimilation and disassimilation of the tissues—consists entirely in this fact. Gautier holds that if the tissue-transformations in inferior animals are almost wholly *aërobic*, the tissue-transformations of the superior animals are, on the contrary, *anaërobic* in a notable proportion. According to conclusions hitherto accepted, this looks something like assumption, and seems paradoxical besides, but he carefully attacks the problem, and we think successfully; the force of his conclusions, whether we regard them practically or theoretically, amount to demonstration.

Tissue-Transformations in the Superior Animals.—Investigating on the lines here indicated, he has been enabled to show experimentally, that while four-fifths of our internal combustions are the result of a veritable *aërobic* process analogous to, if not identical with, the oxydation of alcohol under the influence of *mycoderma vini* or *aceti*, the combustions, secretive and excretive that remain—to the extent of one-fifth—are produced at the cost of the tissues themselves, independently and

exclusively of foreign oxygenous intervention; in other words, that a portion of our living tissues comport themselves precisely as ferments *anaërobic* or putrescent do. This point attained, he was naturally led to infer that, if the intimate organic life of such portion of animal tissue of cellular aggregates is independent of oxygenous supply from atmospheric sources, it resembles the bacterial ferments in the mode and manner of assimilating and dis-assimilating organised material, and we ought to find in the products of secretion and excretion, those substances that are to be met with in an *aërobic* albumenoid fermentation—that is, the putrefactive fermentations; and he shows, as a matter of fact, that this is so. In the normal secreta and excreta are to be found the whole of the products of putrefactive processes properly so called—such as carbonic acid and ammonia—in part free, in part in the form of urea, salts, phenol, endol, scatol, of our fæcal and urinary excrementa; the butyric, acetic, and other superior adipose acids; the lactic, succinic phenylactic acids of our muscular tissues, and in the glandular and renal secretions. In the processes of putrefaction, nitrogen, sulphuretted and phosphuretted gases, together with the hydrogen of the intestinal canal, are also to

be met with. The identity is consequently complete, or nearly so, and he very logically asks, why ought we not to suspect and be able to detect the presence in the urine, glandular secretions, muscular fibres, &c., of these toxic alkaloids, whose history forms the subject of the remarkable *memoire* he has recently submitted for the benefit of scientific workers?

He has here unmistakeably ascertained their existence in operating in a wide area of animated nature; venoms, salivas, various glandular secretions, those even of the silkworm receiving close examination. Devoting special attention to study of these in relation to the muscular tissues in the blood of man and the mammalia generally, he draws attention to the fact of the perceptible increase and accumulation of these alkaloids in the circulation, when from any cause the bowels, kidney, liver, skin, &c., flag, or become defective in their functional activity. He has further insisted that it is under these circumstances that they are permitted to exert their toxic action on the nervous centres, and so give rise to a great variety of morbid phenomena whose determinate successive development and combination, when considered as a whole, make up the portraiture of particular cases or classes of cases of disease.

For those who give attention to the conservative character of our economic physiological principles, but know little of the organism's liability to perversion and deterioration by its own inherent forces, it will be pleasing to see how Gautier proceeds to show in what way in health a normal balance is preserved, how the body escapes disturbance and disintegration by processes purely auto-infective which are ever ready to declare themselves.

THE PROCESSES BY WHICH AUTO-INTOXICATION IS RESISTED.—Gautier goes on to show that the organism is enabled to resist the incessant dangers from auto-intoxication by two distinct methods: first by the separation of the effete toxic elements, and their destruction by oxygenation more or less efficiently. Elimination by the kidneys more particularly betrays this fact, and this he strongly urges, for he has almost invariably found slight traces of ptomaines in the normal urine; very slight, it is true, some would even deny their presence, but it is attested by others besides himself, as also by the fact that they increase and become considerable in quantity in many pathological conditions. Creatinine, for example, has been extracted in cases of uræmia. Their elimination by the bowels seems to him just as certain;

though here, by reason of the difficulties of examination, it is less capable of demonstration.

The process which enables the economy to resist auto-intoxication from the alkaloids, and which he holds to be more powerful than elimination, is their incessant combustion in contact with the oxygen of the blood. For the most part, those deleterious compounds are markedly oxydizable, and it is under the vivifying influence of the incessantly maintained supply of oxygen that they consume themselves and disappear, at least in part, facts which sufficiently explain why—under normal conditions—only traces of the muscular leucomaines are already detected in the urines ; in large proportion they having undergone combustion in the current of the circulation, if not in the tissues themselves.

In any case, if from any cause whatever the free and normal aeration of the blood is interfered with, or materially diminished, Gautier has always found the quantity of hæmoglobine decreased, as in anæmia and chlorosis, and should there be introduced into the blood, substances which interfere with the *hæmatose* or blood formation, immediately materials of the ptomaine and leucomaine order are generally found accompanying them. The appearance of

the allantoine in the urine of dogs, whose means of respiration has been gradually reduced—according to Frerichs and Stadeler—and the reality of asphyxic glycemia—according to Daster—is evidence of the fact.

The Practical Bearings of the Subject on Medicine.—The physiological researches of Gautier as a chemist—fortunately for us—have taken a most important direction. Both as regards their special application to pathology and practical medicine, it is impossible to ignore the great value of his work to medical science. Labours in this direction have been considerable but far from exact. Gautier's contribution will do much to remedy our position, and afford an explanation of the morbid phenomena we are daily called upon to deal with, and yet know but little of essentially. As examples of this take the nervous disturbances associated with anæmia, chlorosis, pregnancy, and the beneficial effects derived in such cases from the inhalation of pure air. Oxygen, for instance, is often the sole means known for combating effectually the persistent vomiting which arises from the retention of imperfectly burnt, or imperfectly eliminated, materials in the tissues or the blood. Again, is it not admissible for us to ask whether fever itself—which is coincident with the

smallest alimentary consumption, and an inverse proportional increase of carbonic acid eliminated and of oxygen consumed, with acceleration of the circulation to boot—may not have for its physiological aim and object the destruction of these deleterious substances which, under certain conditions, are formed, or form themselves so abundantly in the economy?

Thus far it has been no small pleasure to follow Gautier in his lucid inductions. And much averse as he is to venturing beyond the limits justified by a judicious scientific spirit of inquiry, based on data that are positively reliable, it only remains for us to acknowledge that to him belongs the largest share of merit in having indicated—without deducting all the pathological and therapeutic consequences legitimately available—the principles of those beneficent agencies which excite the functions of the kidneys, skin, and intestinal mucous membrane, and, what is still more important, the necessity of the constant disinfection of the economy by all that promotes the processes of respiration, and *hæmatose*, in other words, renewal of the healthy blood.

It only remains to be added that the work of Gautier is not yet completed. He feels convinced that however actively poisonous to the

animal economy the alkaloids we have been dealing with may be, there exist azotised substances non-alkaloidal which accompany them, and are endowed with activities still more remarkable. He points out that Panum's septic poison contains little or no alkaloid ; that the extractive and crystallisable matters are extremely toxic : furthermore, the essentially active principle of the venom of snakes he believes is nitrogenous but not alkaloidal. These substances are in other respects more important quantitatively than the ptomaines and the leucomaines oxydisable and azotised like them, and require that they should be studied still more closely than they have yet been. He expresses the firm conviction that their investigation will prove one of the most instructive sources reserved for the medicine of the future.

II.

A New Departure in Pathology.

In his recent *Mémoire* Peter affirms that his object is to draw upon traditional medicine in confirmation of the medicine of the future. In other words, he desires to advance the facts of observation in support of the beautiful researches with which Gautier is now enriching medicine as a science. These researches, apart from their chemical and medico-legal value, he affirms, have the important merit of confirming what we already know of the intoxication of the animal economy with its own products; whilst, at the same time, they add to our previous knowledge and to pathological investigation a greater degree of method and precision.

But what are really the terms of the questions involved?

Gautier informs us that in dead animal tissues undergoing the process of putrefactive decomposition, there are elaborated the alkoloids which Selmi called ptomaines. He further in-

forms us that in the living animal tissues, and by virtue of their vitality, there are elaborated alkaloids which are analogous to these. Some of these he has discovered, and he names them leucomaines. This is not all; he has ascertained that in the living animal economy there are also elaborated azotised uncrystallisable substances which are still undetermined, and which are the extractive matters. In addition to this, we are assured that if the ptomaines are toxic, the leucomaines are also toxic, and that the extractive matters are more toxic than either.

So much for the chemical aspect of the question. Now comes the clinical one.

Here he has unquestionably discovered that according to the different sources of intoxication, there is a corresponding indication. Intoxication by the extractive matters is accompanied by hyperthermia, whilst intoxication by the animal alkaloids is accompanied by hypothermia; that in the living organism a variation or succession of extremes in temperature may manifest itself, according to the combination or alternation of poisonings by these deleterious physiological products. But what is of additional interest, and must be gratifying to many to learn in connection with Gautier's re-

searches, is the fact of their emancipating us from the tyranny of micro-germism. They explain the formation of poisonous alkaloids and still more poisonous extractive matters, by means alone of the physiological processes continually at work. He discloses the fact that in auto-intoxication, the spontaneous or self-infection of the living organism by the alkoloids and extractive matters, there is, by reason of their essentially normal physiological origin, no question of quality but simply one of quantity to be considered; that, in other words, the healthy living organism may become poisoned by the accumulation within itself of deleterious substances normally elaborated but imperfectly or defectively eliminated.

The important question then presents itself—in what way does auto-intoxication or spontaneous infection of the economy take place? And here a word or two regarding life may not be superfluous or out of place. Life Gautier regards as a phenomenon essentially relative and contingent; it is a series of partial deaths; the organism only lives on condition of incessant elementary disintegration; we bear about with us, within us, the effete *débris* of our living selves. That phase of it called health is a phenomenon quite as relative and contingent, and

may be regarded as life's equilibrium between organic good and evil. Normal health is conditional on an incessant transformation and elimination of the effete or old organic material which has to give place to renewal by the new. Nervous phenomena, central or peripheral, may modify the phenomena and so complicate the fact, but nothing can do away with it.

The series of partial deaths which constitute life is the result of organic functional operations. When thought is evolved the brain generates heat, and the material product of the cerebral action is neurine, an alkaloid prejudicial to normal life ; when movement is exerted heat is evolved, and the material result of muscular action is the creatine, creatinine, and still other alkaloid congeners, which Gautier proves to be equally prejudicial to the health of life. The tissues and organs perform a function of disintegration, and in the process they fabricate those alkaloids and extractive matters which must be regarded as veritable scoria, resulting in the processes of physiological combustion of the elements of the organic tissues. The organism is always dying, and, strange as the paradox may sound, could not live unless it died. We thus perceive how precarious a condition is that which we call health, and why, by

the modifications of the organism in vital activity, disorder or disease may manifest itself in consequence of the simple accumulation of cadaveric materials.

It has been clearly shown, and must now be freely accepted, that the animal alkaloids are a necessary product of vital physiological processes ; this is both synthetically and analytically proved by Peter and Gautier, who press the important fact with all its consequences on our attention. In 1881 Gautier announced that there were to be detected in the excretions of living animals in good sound health, as well as during disease, substances of the nature of ptomaines. Since then he has abundantly confirmed the fact, and further announced that about four-fifths of our disassimilations are the result of veritable internal combustions, *aërobic* transformations comparable to the oxydation of alcohol under the influence of *mycoderma vini* or *aceti*, and that the remaining fifth of the disassimilations are formed at the expense of the living tissues themselves, free of all demands on foreign oxygen ; in a word, that a fifth part of our tissues live after the manner of ferments *anaërobic* or putrefactive. Confronted with these facts, and studying their organo-chemical bearings, he was naturally

forced to infer that if the essential life of that portion of the animal cells grouped in tissues and living without oxygen derivable from atmospheric sources, is analogous to the bacterial ferments in the mode by which it assimilates and disassimilates the organic elementary material, we ought to be able to detect in the animal secretions the substances themselves which characterise and constantly accompany *anaërobic* fermentation of the albumenoids, and this Gautier was happily enabled to demonstrate to be really the case.

All this should not surprise us. If the animal economy is not purely a chemical apparatus, it is far less a fermentating vat. It therefore requires no imaginative license to conceive of alkaloids being formed within the living organism and independent of bacterial fermentation, though somewhat resembling it. Do we not every instant of our lives, and quite normally, elaborate acids and bases, not merely carbonic acid, but uric acid? Uric acid is a product of animal life, and one which is inconceivable apart from it. Do we not spontaneously and normally fabricate bases such as urea, which can combine with azotic and oxalic acid, and which, by simply splitting up chemically, may go to the formation of carbonate of

ammonia? Such being the case, why then should we not admit that the living organism—which by virtue of vital activities, by means of the living and acting cells, and in the absence of all bacterial intervention, is capable of fabricating urea—is also capable of fabricating various alkaloids? That which might seem *a priori* evident, is now bio-chemically proved to demonstration. Undoubtedly it is in consequence of the splitting up of disassimilations, brought about at the expense of the tissues themselves, and in contact with oxygen, that all the disintegrative phenomena are accomplished in the animal economy, and by the physiological activities of animal cellules grouped in tissues.

According to Gautier, we resist auto-intoxication by two modes or mechanisms—by the elimination of the toxic products, and by their destruction by oxygenation. Elimination is accomplished by the kidneys and the liver. As to their destruction, this consists in a continuous combustion of the leucomaines by the oxygen of the blood; the leucomaines are there burnt, consumed in the circulatory current, and it may be, partially in the tissues.

Accumulation may take place under two widely different conditions; as when there is excess of extractive matters and alkaloids, with

normal but inadequate emunction, or when the production of deleterious materials is normal, but emunction insufficient, the emunctories being diseased or deranged.

Gautier affirms that auto-intoxication may thus result from excessive production and inefficient emunction—the emunctories however remaining sound. Peter teaches that this is what we observe in physical over-taxation, over-exertion, a condition which he graphically illustrates: "It was in 1852," says he, "when entering on my clinical studies, and ardent in my attendance in the clinique of Chomel, I was witness of the following instance: A young man was received under the celebrated professor's charge, suffering from prostration, muscular pain, and rachialgia. Chomel made the examination with all the care and attention usual with him, then, as also usual with him, in the presence of the patient, he gave the diagnosis in Latin, which was—*aut febris peyerica, aut variola incipiens*—it is either typhoid fever, or incipient small-pox. I felt rather dissatisfied to hear a diagnosis so little precise pronounced by one so eminent in his art, and yet how very correct was he in this. The truth of the matter was, though Chomel was not aware of it, this young fellow, in a state of destitution, had

walked from Compiègne to Paris, sleeping by the way-side at night and nourishing himself with such refuse food as chance supplied.

"It was under such circumstances the patient had developed febrile symptoms. The day after his admission, and simply from rest in bed, he felt better, and the day following he was altogether well. Simple rest had enabled the muscular system, and economy generally, to rid itself of the proteid embarrassment resulting from the functional combustion of the tissues. His ailment was merely the fever of over-taxation, brought on by the accumulation in the system of material elaborated in excess, and consequently inefficiently eliminated; the temporary poisoning of the system had lit up the fever of prostration. So much for the hesitating diagnosis, *febris peyerica;* muscular and nervous pain expressed itself in rachialgia, so much for *variola incipiens* included in the same. Now supposing that in this given case, the elaboration of extractive matters and alkaloids we take to have been as ten, and the eliminated as eight, we have a storing up of two. But supposing, on the other hand, that instead of walking from Compiègne to Paris in two days, the patient had walked from Marseilles to Paris in twenty, instead of storing up twice two he

would have stored up twice twenty, and consequently instead of a simple attack of toxic over-exertion, auto-infective fever of short duration, he might have suffered from febrile intoxication, more complete, more persistent, and more serious; he would in all probability have developed the typhus of the soldier on a harassing march."

It is in this way, making due allowance for massing of men in large bodies, that the typhus of armies originates and spreads. In this case there is a co-operation of auto-typhusation with hetero-typhusation. For those who are in the position of observing and appreciating such facts, says he, it is scarcely possible to escape the conviction that there exists a morbid series, which is as natural as it is evident, leading from the simple form of fatigue-fever to that of typhus, which is the highest expression of the poisoning of the organism by itself, or by contact with others under conditions such as now referred to. It is consequently something like an absurdity to introduce micro-germs into the question. The specific microbe has yet to be discovered. It requires, he thinks, no such flight of fancy as to suppose microphytes waylaying armies on the march, and no such dream of rank and file conveying them in their haversacks or cartridge boxes.

For the military medical officer who has seen this form of typhusation develop itself, its origin is not to be doubted ; it accompanies prolonged fatigue, over-crowding, and privation generally. He would no more question it appearing spontaneously than he would its being contagious, and as this is based on observation also, he is forced to admit the view, apparently irreconcilable, of spontaneity and contagiousness. What is true of fatigue fever and typhus fever is equally true of typhoid fever, in the spontaneity of which all physicians of a certain age who have had opportunities of observing it extensively, are convinced. Does this imply its non-contagiousness, or that a spontaneous attack of A may not be communicable to B ? On the contrary, all know it to be very contagious : whether it have as its agent of transmission the bacillus of Eberth, displaced by that of Gofiky and Artaud, and this in turn to be displaced by some other future bacteride, matters little.

What Peter insists on chiefly is the existence of a natural typhoid morbid series, in which ordinary typhoid fever stands between the simple fever of over-taxation and typhus properly so-called. He tells us that when occupying the chair of medicine for Gresolle at the Faculty of Medicine, in 1869, he taught the doctrine of

auto-typhusation, using this term to clearly define the nature of the accidents, the principal of which are in all cases hyperthermia, innervation and hæmorrhages. In his *Clinique Médicale*, he points out that typhus may arise in various ways, and illustrates the question by its appearance in the navy, army, prison, and hospital establishments. Under such conditions there is unquestionably inhalation of morbific matter, organic emanations, productive of typhoid vitiations. But what does it matter, he asks, whether morbific matter finds its way into the organism from without, or whether it is elaborated from within? The individual suffering from attack is none the less contaminated because he is self contaminated, and this is what Peter calls auto-typhusation, no matter what the form may be. Should functional disturbance cause difference in some respects from typhus of a given type, difference in morbid phenomena will depend largely on the various toxic elements in the blood, and here must be sought the explanation of the modifications of the distinctive forms, putrescent, cerebro-spinal, biliary, atheramic, or uræmic. The etilogical factor extends to all the typhoid morbid series in all such maladies; he insists on the presence of an animal poison of cadaveric nature in the living

organism, either communicated from without or originating from within, but not eliminated—an organic product so highly prejudicial to life that it disturbs the vital activities of the living organisms with which it comes in contact, and this quality is what constitutes infection. The systematic expression common to the etiological factor is the stupor, τῦφος, typhus. Again, the difference in species of the animal poison constitutes the difference of the typhus in such a way that in every form dependent on this cause we observe facts of innervation, but in each form presenting something specifically different. In the common and ordinary form the dominant nervous factor is the delirium; in the cerebro-spinal it is the tetaniform; in the typhoid it is the coma and delirium; in the biliary or cholemic the delirium and convulsion; in the uræmic it is the coma and convulsions, that is to say, the eclampsia. Nor must we omit that the other pathological factor, hæmorrhage, is common to all the typhoid series; of their association from the simplest form of epistaxis to melæna it is needless to be reminded.

Inefficient elimination while the emunctories are sound is only one aspect of the question; but supposing the emunctories are diseased, supposing the kidney in particular permits of percola-

tion of the serum of the blood, its albumen, then we observe another series of accidents embraced under the term uræmia, and which to Peter constitutes typhusation, for in proportion as the cypher of albumen increases in the urine, that of urea and extracted matters diminish ; that is to say, the non-eliminated extractive material retained increases in the blood. This Quinquand has abundantly demonstrated. Nothing is more simple ; in replying on the data which explain the clinical facts in appearance contradictory—that is, that in certain cases of uræmia there is to be observed an elevation of temperature, and that in certain other cases the temperature is sometimes stationary, at others it falls—nothing is easier of comprehension than that if there is an accumulation of extractive matter in the blood we detect hyperthermia ; if there is accumulation of the alkaloids, there is, on the other hand, hypothermia ; but should the two factors co-exist they neutralise each other, and the temperature remains stationary. Let one or other turn the scale, and immediately a thermometric variation may be noted. Add to this the typhoid accompaniments, perturbation of the nervous system and hæmorrhagic accidents. If, again, it is the liver which is the seat of the functional disturbance,

or is so structurally affected that elimination is incomplete, and that there is cholemic typhusation, then we shall have also elevation of temperature, innervation, hæmorrhage, and disorders the most varied and serious.

Here it is my duty to mention the independent views of Professor Ravilliod on this subject. He described under the name of *extratihemie* the numerous cases of over-taxation, fatigue, fever. Now what is curious is that sometimes the patients present the symptoms of typhoid fever, sometimes those of endocarditis, and sometimes even those of acute albuminuria ; that is to say, that there is present, in sketch or outline as it were, the types of the morbid series of which I have spoken. And what is not less interesting in the close and precise observation of Professor Ravilliod, is the fact that recovery, when it takes place, does so in consequence of veritable breaking up and rout of the urates and probably the extractive matters ; that is to say, that ailments cease by a disembarrassment of the organism.

What Peter chiefly insists upon is that here clinics and biochemics are in accord in showing that the morbid accidents are the effects of the same cause—which is auto-typhusation.

I shall now briefly deal with the question of

intoxication by the alkaloids, that is to say, those cases in which hypothermia is present. In Germany it is known by the term *botulism*, a form of poisoning of the organism observed to result from the ingestion of putrefying meats, pork sausages in particular.

What in reality are aliments of flesh or meat origin if they are not dead animal material? If fresh they are wholesome, if in process of putrefaction they cease to be so—why, and in what way, both Selmi and Armand Gautier have made known to us. It is by reason of their containing cadaveric alkaloids—the ptomaines. This being the case poisoning exhibits itself in the form of cholera, by diarrhœa, vomiting, cramps, algidity, &c. This is evidently induced by the ptomaines which have been elaborated in the articles of animal diet in a progressive state of decomposition. Poisoning of the kind has been observed in France as elsewhere. It will suffice to mention that case in which the scientific penetration of Peter's colleague, Brouardel, was so happily verified. A whole family presented symptoms of poisoning; a crime was suspected. There was nothing of the kind however. It was simply a case of poisoning, the consequence of indulgence at a family fête in stuffed goose, but stuffed goose

too far gone, too high. Brouardel and Boutmy both detected analytically the presence of cadaveric alkaloids, the ptomaines of putrefaction, in the *débris* and ingesta.

In all such cases there is hypothermia, precisely as is to be observed in ordinary poisoning by tartar-emetic or arsenic. In cholera, which presents such close analogies, the same is manifest; diminished temperature, algidity, accompanying digestive troubles—all play a prominent *rôle* throughout. Who will not admit in those affections poisoning by a toxic alkaloid, alkaloid of putrefaction,—or refuse to see that nutritive ingesta may give rise to the formation of toxic alkaloids? Whether the alkaloids are produced or administered may involve a question not always easy to decide, but in either case there can be little doubt as to the choleraic nature of the poisoning. Guided by facts such as these, it requires no speculative or scientific licence to conceive, for we can actually trace a morbid series of a very natural order leading from *botulism* to Asiatic cholera. We are, in fact, justified in holding that there are in pathology morbid series, as legitimate as those observed in chemistry, geology, palæontology, or botany. Nature does not proceed by leaps but by gradations; she proceeds from the

simpler term to the more complex; each having an existence of its own, but presenting in its terms antecedent and succedent analogies, which are the bonds of union in the series, while each preserves its stamp of individuality.

It is a pleasure to note, in closing these remarks, that Gautier has approached these problems of life not only as a chemist but as a physiologist; what is more, he has given prominence to the fact that the animal alkaloids can be elaborated by the spontaneous physiological processes of life. It is very apparent that we have in this view a partial return to humoralism, poisoning by soluble alkaloids being in reality nothing short of poisoning by an organic liquid which has undergone change, in a word, deterioration, and, that this spontaneity goes on in health as it does in disease is equally established by the chemical demonstrations of Gautier, and the chemical observations of Peter.

A few words in conclusion. Scientific missions inspired in the interests of germ pathology have visited Egypt, India, and Southern Europe, in the quest of a specific microbe; they have signally failed. Dr. Koch, the leader of one of them, thought he had found the pathogermic entity, but confronted and constrained by facts, the learned bacteriologist has felt himself

obliged to admit that the said bacillus does not directly engender cholera, that it can only do so indirectly and by the intervention of a ptomaine which it secretes. But this implies two suppositions : firstly, the existence of the specific bacillus which Koch has not discovered ; secondly, the supposition of the secretion of the ptomaine by that bacillus which Koch is just as far from discovering.

Hypothetical assumptions may easily be carried too far. Something simpler and more evident is needed to justify the theorising mania, The German physician, Koch, assumes ; the French physician, Gautier, demonstrates ; he shows the spontaneous elaboration of the ptomaine-leucomaines in the living organism, —demonstrates the formation of these leucomaines by the splitting up of disassimilations, —demonstrates that these chemical divisions are accomplished by the vital processes of the living cells ; that these processes are peculiar to the living organism and altogether independent of the intervention of vegeto-micro-organisms ; Gautier also demonstrates their toxicity and the mechanism chemico-dynamical by which the healthy organism escapes intoxication and disease. Can the medical mind henceforth hesitate between pangermic doctrines

bolstered up by hazy, vague hypotheses, and the doctrines we are maintaining, which are clear and precise, and which explain the phenomena of life, normal and abnormal, by life itself in action? Obviously not. Let us now proceed a little farther, that what is here evident, may become self-evident.

Auto-Intoxication

In Disease.

PART IV.

If the student interested in pathology, and more particularly pathogenesis, may well exclaim—Where are we now?—the practitioner of thirty years' experience may safely assure himself that we are pretty much where we were before. The speculative gropings of the period above-mentioned may have added some brilliant pages to the romance of medicine, but very little to our knowledge of disease and still less to its alleviation or cure. It must now be evident to many thinking minds that the so-called scientific method in medicine is no substitute for judicious observation, seeing that mathematical accuracy is out of the question. Precision in medicine is possible only in the direction of the fact realised—that is to say, in the evidence of physical alterations of living substance, as seen in lesion and its signs. As to the morbid act, that is to say, disease in its evolution, it escapes all efforts at precision, for the simple reason that the act which is the *to be* is always subordinate to the vitality of

the organism affected, and so necessarily dependent on the forces of that organism and infinitely variable as these forces themselves.

Chiefly due to Lœnnec, instrumentation has gradually usurped the place of observation and the unaided senses. The stethoscope has suggested the still increasing list of scopes, and the microscope has long been thought essential in the autopsy of the living as well as of the dead body wherever morbid results, processes, or even causes are in question. The examination of all that is physical in the phenomena of life is doubtless of much importance in pathology ; mathematical precision may even be desirable, but only, be it observed, where precision is possible, that is, in the domain of the physio-chemical phenomena of life, in the domain of accomplished facts. In the order of dynamical processes it cannot be reckoned on. In medicine the danger which it threatens is a disregard of clinical observation. The undue study of lesion is liable to lead us to lose sight of the patient, and to indulge in estimates, illusory and incomplete, and of the malady as a whole from which the patient may be suffering. It is the living organism as a whole reacting on itself that we chiefly have to deal with in disease.

This great guiding principle has been lost sight of. The change of method has led to change of doctrines, and wondrous is the history thereof. The generalisers of disease became localisers of disease, and now we witness another transformation, wherein ardent supporters of localisation are becoming equally ardent for generalisation. Having confined a given malady to a given organ, then to some part of its parenchyma and later to its elementary cells, they have finally displaced it altogether and find in the alien microbe the cause and essence of the morbid evil. For example, pneumonia which used to be regarded as a general affection with a local pulmonary manifestation, became in the hands of the precisian pure inflammation of the lungs, a disease of plastic exudation. Histology, triumphant for a time, cellular caprices monopolised the attention ; finally the morbid micro-germ found favour and the pneumono-coccus was discovered. But anatomical pathology, anatomical histology and bacillography do not exhaust the phases of the study of this illustrative malady. For some reason or other the pneumo-coccus is not permanent, not pathognomonic of pneumonia. It would appear that the pneumono-coccus may become an

endocardo-coccus in endo-carditis, or a meningo-coccus in meningitis ; thus it loses all claim to specificity, and now we are in the presence of another transformation ; from humoralism we have passed to solidism, from solidism we return again to humoralism, and the microbe is only the connecting link. The first authorities, Pasteur, Koch and Brieger are now convinced that the cocci, as we have already pointed out, are not dangerous in themselves, but only through certain deleterious matters which they give rise to in the animal economy.

Investigation is now in the direction of the animal alkaloids and their effects. The researches of Brieger have most important bearings on the subject. His recent work abounds in views and facts, which to some extent were utilised in our first edition. The author endeavours to demonstrate the great importance of the relations that exist between the three orders of study, microbes, ptomaines and maladies, supporting them by a series of investigation rigorously carried out according to methods of his own, and exposes the fact that microbes have the property in the course of action of forming nitrogenous bases of chemical species perfectly defined, and he then proceeds

to show that these alkaloids, even in the minutest quantities, are capable of giving rise to disorders more or less serious, and even to death itself—disturbances which frequently present relations analogous to those observed in the course of well-known infectious and other maladies. Researches on these lines Brieger has applied to septicæmia, where the tendency is in our day to award the preponderant *rôle* to chemical phenomena accompanying bacterial invasion.

Leading theorists loudly attribute to microbes the power, very enigmatical, of engendering maladies, but until now imperfect chemical processes have been employed with a view to clearing up the mystery that envelops these pathological properties. The subject is, however, of the highest importance to the clinicist, as indicated by the morbid phenomena which present themselves in the course of experiment. Abnormal temperatures, functional arrest, weakening of the mental faculties, disturbance of the most important acts of nutrition and digestion—all force us to admit that in morbid conditions the organism is profoundly affected by abnormal chemical activities. Brieger points out, for instance, that the organism attacked with septicæmia is the theatre of chemical phenomena of an order very different from that

which exist in the healthy state. He finds very striking evidence of this in the increase of phenol eliminated in the case of certain infectious maladies, such as diphtheria, erysipelas, pyemia, and scarlatina, but at the same time repudiates the hypothesis based on intestinal putrefaction, which was admitted in cases of such maladies; and he confirms the fact that typhoid maladies, whether abdominal or recurrent, develop themselves without increase of phenol in the urines, irrespective of relaxation or constipation of the bowels. He further shows that in the greater number of cases of scarlatina observed by him this product increased during the period of the eruption, whilst, on the contrary, it decreased in the corresponding period in the case of measles. Yet we know the close resemblance of these maladies. He observed the same in erysipelas and pneumonia, and thinks it to be therefore erroneous to suppose that intestinal fermentation plays a part in, or has anything to do with the matter. Thus it follows that the marked augmentation of the normal products of elimination which accompany infectious maladies justifies the conclusion that there are parallel gradations of consecutive chemical phenomena going on—processes of infection—and which are certainly not putrefactive.

It follows that the figured species of the cocci, bacilli and the rest are now of little consequence ; it is the physio-chemical processes which they initiate that is all-important in the problem. The microbes are now discovered to be merely the porters, the carriers of disease, in infection. But how they act under the new conditions is the question. Formerly they were supposed to act mechanically on the mass, by emboli, &c., or traumatically by destruction of the living cells or organs by some more delicate physio-chemical action, as depriving the hæmoglobine of its oxygen and thus causing asphyxia ; but according to each hypothesis the microbes acted *per se*. Now all is changed. Leading bacillographers admit that it is not the bacilli but the animal alkaloids which their action gives rise to, or genders, and these in turn become the object of research. The cultivation liquids of the particular form of bacilli associated with all these particular maladies specified now undergo chemical investigation with a view to the detection of the alkaloidal poisons, and apparently with much success.

But leaving germ-pathologists to exploit their new position, we must insist that the phenomena of disease, even to the most essential processes, are possible without the intervention

of micro-organisms, bacillar or otherwise? And why not? Seeing there are so many diseases without them, such as hydrophobia, to begin with? The term animal alkaloid has been sufficiently explained. Those vital, or leucomaines, having been discovered to be true poisons which are formed during the transformations of the living cells, are liable at all times to lead to auto-intoxication, if we had not the power of getting rid of them by physiological combustion and excretion. Gautier has succeeded, as we have seen, in isolating some of the agents which the healthiest of them are ever producing, as xantho-creatinine and cruso-creatinine, for example. Some of the maladies attributed to this cause we have already indicated: uræmo-typhus,—uræmia, cholotyphus,—fatal jaundice, athero-typhus,—ulcerative endocarditis, puerpero-typhus,—puerperal fever, and the like.

It is surprising that such poisons should result from healthy cell life, but the venom of the cobra is analogous. Their presence has been demonstrated in the breath even by Brown-Sequard and Arsonval, and also in the perspiration and the urine without any accompanying trace of microbes. The clinical observer ought then to turn attention seriously

in this direction, and while trying to get rid of the new errors, add to the store of old truths. The clinical teaching in vogue for some years past has become altogether speculative, is incapable of affording a correct or adequate conception of the nature and mechanism of disease. This is not denying some indebtedness to the efforts of eminent experimentalists in hazy regions of germ-pathology. But we must not forget bio-chemical elements which occupy the most important part in our analyses of disease. Neither in the teacher, far less in the practitioner, should theory usurp the place of careful clinical observation. Here it is above all where the claims of nature and art in the cure of disease can be made evident with satisfaction to ourselves and also to the patients.

I.

Latest Investigations and Results.

The new departure in pathology finds an able exponent in Professor Bouchard. This eminent teacher, by the publication of his course of lectures, must now be regarded as heading the movement. Medical investigation, if it has not undergone complete transformation, has, it must be frankly admitted, changed its objective; having been successively directed to the study of symptoms, anatomic lesions, and anatomical pathology, it has now as its chief aim physiological pathogeny. If this new direction of research has its speculative dangers, it nevertheless promises a future brilliant in positive results. As I have elsewhere shown, it conducts analysis of morbid phenomena with a view to ascertain how far they may be productive of or dependent on the action of material obnoxious to nutrition and nervous reaction, and to demonstrate that, whether introduced into the system from with-

out or resulting from perversion of metabolism, secretion, and elimination from within, these poisonous principles explain the origin and mechanism of much of what is called disorder and disease. As the reality of auto-intoxication and auto-infection of the organism abounds in novelty and interest, and is every day receiving more and more the attention of the practical pathologist, a notice of the subject in relation to the lessons of Professor Bouchard may be welcome to the studious practitioner, who may have little opportunity of sifting his well-stored page for himself. The pathological field which the survey covers is sufficiently comprehensive. Recognising disease as arising from four leading processes, Bouchard commences by observing that man constitutionally and naturally possesses in himself much that is both potentially and actually morbid. His vital condition may be abnormal—in other words, nutrition may be defective ; its vitiations or derangements being either hereditary or acquired, we have maladies of antecedent nutritive disturbance. The organism may be morbidly affected by external causes, physical, mechanical, or chemical, as by wounds, burns, poisons—causes which, by operating directly on the cells, excite immediate reactions. These

pathogenic processes, we know, rarely remain simple ; they are rendered complex by reason of mere reflexes. External causes may also act on the economy indirectly through the medium of the nervous system, and it is by that pathogenic process that maladies which Bouchard calls maladies of nervous reaction, are developed. Finally, the economy may be invaded by contagious or infectious elements, however these may be causally regarded.

It may not always be an easy matter to distinguish the *ens mali* from the *agens mali* in disease. Bouchard, though subscribing to the theoretical import of a microbic *rôle* in etiology, unquestionably shows that as yet its range is very limited, and leaves things pretty much as they were. In the vast variety of ailments man is heir to, some, we know, are contagious or infectious, or are liable to assume that character. His method of investigation, however, clearly discloses the fact that whatever the essential nature of contaminating elements may be, the more their operation on the organism is observed, the more evident it becomes that the vito-chemical processes involved, and their modes of manifestation are in no wise exceptional. Organic reaction is the law of disease, whether its processes are destructive or con-

servative in their issues. It is always with the nutritive and sensible nervous reactions that pathological inquiry properly commences.

Intoxication when acting primarily, that is, directly, Bouchard includes in the four pathogenic processes, but he upholds conclusively the view that the process of disordered nutrition, as well as those of nervous reaction and contagion or infection, may also cause intoxication; if in a secondary mode, that is, indirectly, and he instances gout in those of flabby habit, accompanied with listlessness, depression, indisposition to exertion, and the like. In the renal, cutaneous and pulmonary secretions of such are detected incompletely oxidised products of disassimilations, such as oxalates, volatile fatty acid, &c. Substances, which it may be reasonably assumed in some way set up the nervous symptoms, and thus supply a tracing sufficiently indicative of intoxication due to antecedent nutritive disorder. Again, in subjects ordinarily healthy, the same deleterious substances, by excessive accumulation or imperfect destruction, in consequence of loss of sleep, mental anxiety, bodily fatigue or defective hygiene, may induce the same result, and are quite as clearly outlined. Again, in the case of the more pernicious maladies, whether arising infectiously

or not, among substances elaborated, some are powerfully toxic even in small quantity, and are analogous to those which are the product of the putrefactive processes, and may become pathogenic agents of systemic poisonings. Bouchard cites in illustration septicæmia. If in such case, says he, the malady is accompanied with no important organic lesions, if lesion is confined to the cellular tissues of the region affected, such as he believes is generally the case in septicæmia, we naturally attribute the general accident to the absorption of toxic materials, alkaloidal or otherwise, elaborated in the course of morbid action. We can hardly understand their having any other origin. To all appearance, then, there are certain classes of disease in which infection leads to secondary intoxication. But, even in normal physiological conditions, and in the best of health, the animal organism is a laboratory and receptacle of what is poisonous. It develops them in disassimilation and secretion. The animal economy is thus the theatre of toxic evolution and elimination—phenomena which are even brought about by putrefactive processes, and which are always normally present in the fæcal contents of the intestines. Fæcal putrid products defectively eliminated in the course of health, as in disease may be ab-

sorbed and induce intoxication. It is in this way Bouchard accounts for many accidents which accompany dyspepsia and intestinal inaction.

Seeing the importance of the part played by disordered nutrition, nervous reaction and the putrefactive infectious processes continually at work in the economy, we are brought face to face with the luminous conceptions with which Armand Gautier more particularly has enriched modern medical science. We are confronted with physio- and bio-chemical processes of animal organic growth and decay, their chemical products, particularly those now known as the ptomaines and leucomaines, and finally with the grand facts that in life as in death, apart from and irrespective of microbic interventional activities, the so-called aerobic and anaerobic processes co-exist ; that in the higher animals, man included, cellular life, to a very notable extent, is independent of inspired oxygen ; that the anatomical elements undergo their transformations and other phenomena of oxidation, but that it is in the organised substance they find it. This is evident from the fact that if we note the amount of oxygen derived from respiration, food and liquids on the one hand, and that returned in carbonic

acid by the lungs, skin, and intestinal excreta on the other, they are found equal. But what of the difference in excess of oxygen by water and carbonic acid? It is obviously derived from the reserve in tissue and cellular elementary combinations. Thus, it is now estimated that at least one-fifth of the vital processes is maintained by oxygen, which is not directly derivable from without, but from within; that the processes of metabolism and disassimilation are in a notable part carried on by processes analagous, if not identical, to those of putrefaction or fermentation. In the removed excreta and ingesta are to be found the products of the putrefactive processes properly so-called. The comparative study of these processes in the physiology of health, as in disease, is consequently necessary from the pathological point of view. The constituent material of organic substances, that is, the cellular elements having served their purpose, break up, and then their effete noxious material products are set free. Passing into the extra cellular liquids the resulting products of disintegrative activities are taken up by the lymphatics and thrown into the blood, in whose circulating current all effete transformed material—that found in the intestines, in part at least, included—finds its way.

Elimination being completed in the process of emunction where the skin, lungs, kidneys, and bowels, perform their respective *rôles*.

Thus, all poisons come through the blood. As we have seen, the blood necessarily disposes of its poisonous accessories through the various organs of elimination, so consumes them in the circulatory current in contact with the red globules. This being the case, can the blood be regarded as otherwise than toxic ? Constantly traversed by noxious impurities it must necessarily and invariably contain toxic elements. Bouchard has shown that it is really toxic, and has succeeded in very closely defining the limits within which it is so ; and this has enabled him to conclude that man would die from poisoning if the blood contained ten times more toxic material than it normally contains. But it is to the plasma that this applies. Its cells, like all other cells of the organism, contain elements potentially deleterious. The constituents, however, can only be set free by disassimilation or destruction of the cells themselves. Some are remarkably toxic and form two orders : the organic, largely alkaloidal ; the other inorganic, mineral matter.

In co-operative combustion and elimination, then, lies the safeguard of the economy. This

physiological conception admitted, its experimental verification has to be considered, say in the kidneys and their functions to begin with. The urine gives the key to the problems of intoxication, and forms the necessary introduction to the subject as a whole. This secretion has always been held as toxic, but of experimental proof of it there was little until Feltz's and Ritter's study of the point. But even their work left much to do, at least in detail. It remained for Bouchard to accomplish it. He found the urine toxic, and set himself to a systematic course of venous injection, conducted on the lower animal ; he ascertained the intensity and variation of toxicity in a given weight of animal substance furnished in a given time, and in this way arrived at the comparitive unity of urinary toxicity present. Proceeding on these lines he has been enabled to give numerical expression to these, and in doing so has endowed pathology with yet another term —*urotoxy;* that is, the standard of toxicity of urine necessary to kill a kilogramme of living substance. It is very singular to read these values, in terms, of living animal matter that may be killed by given quantities of urine under examination ; but it is not an easy matter to detect a fallacy in the procedure, one which promises

a ready method of estimating specific actions of multiple poisonous constituents. By examining the normal urine passed in twenty-four hours he forms his urotoxic standard, and studies carefully the variations of toxicity in physiological conditions, and in various pathological states. In this way he establishes the fact that urine per kilogramme fabricates in twenty-four hours sufficient toxic matter to kill 464 grammes of living substance, or nearly the half of what would kill himself in forty-eight hours, all things equal. Variations are significant, and are dependent, in normal urine, on vital conditions, muscular and cerebral activity, alimentation, sleep, &c., &c. Whilst dealing with familiar phases of investigation, Bouchard presents us with others which are altogether new and startling. He finds, for example, that night-urine is denser and richer in solid material, and always less toxic than day-urine ; that during the hours of sleep man eliminates from two to four times less poisonous material than he does during an equal time of wakefulness or cerebral activity ; further, that the toxicity of night and day urine not only differs in quantity and quality, they are also antagonistic in their action, and neutralise each other. The urines of the sleeping hours are always distinctly convulsivant—stimulant—

while those of the working hours are soporific—narcotic—the organism by this mechanism thus eliminating during wakefulness material, which, if accumulated in the system, would induce sleep, and during the hours of sleep eliminating that which would induce wakefulness, thus opening up fresh lines of physiological speculation and research of the most vital and interesting kind.

But the degree of toxicity of the urine is only one stage of the investigations Bouchard aims at establishing. He carries his enquiries much farther, and dissects them, as it were, examining each of the toxic elements in their chemical, physiological, and pathological relations. By varying his experimental procedure, he has shown that urine contains not one poison but several. In treating urines with alcohol and other solvents in order to separate their materials, with charcoal he has succeeded in disassociating three various toxic elements, and ascertains the fact that there exist at least seven, which may be classed thus: one is a diuretic, a second is a narcotic, and a third sialogenic. There are two other products, one organic, the other inorganic, which are convulsivant; the mineral he finds is potash. Then comes a body which induces powerful myosis—

contraction of the pupil—and which is also met with in colouring matters. Lastly there is an agent which reduces temperature. Analysis of these chemical constituents in their physiological effects are as yet very imperfectly obtained. With few exceptions it has not been possible to isolate them in sufficient quantity for this purpose.

The elimination of such substances rendering the urine toxic, explains why the system escapes their deleterious action. The method and mechanism of their formation now claims a closer examination, especially the co-operative *rôle* of the liver and intestines. The bile which periodically flows into the alimentary canal contains poisonous elements, particularly in the colouring matters; much less so are the biliary salts. Normally, however, secreted bile is little dangerous to the economy, and this by reason of the colouring matter and the salts in a great measure finding their way into the bowels. The intestinal ingesta undergoing putrefaction gives rise to the formation of toxic substances, but in the slow and intermittent passage of the fæces, a part, at least, of the toxic elements is liable to absorption through the mucous surfaces, and finds its way into the *vena porta* where it is arrested, when what is not rejected again into intestines passes into the general circulation.

The alimentary canal is in this way a cause of poisoning to the system, and the question of intoxication from this source has consequently received much attention from observers such as Gautier, Brieger, Mosso and others. But it is to Bouchard we are chiefly indebted for our information. He has taken up the subject, extending it in its physiological and pathological applications more particularly. He has investigated the subject, and shown that alkaloids exist in the fæcal materials; these alkaloids are of several kinds, and that when markedly present in the intestines they are found to be markedly present in the urine also. After Stick, he has confirmed the fact of the toxicity of the fæcal matters. He has examined the toxicity and shown that it is due in great part to potash and ammonia; but that, even when relieved of these elements, they still retain a certain degree of toxicity which must not be disregarded. He shows that intestinal antisepsis, which disposes of the alkaloids of the fæcal and urinary matters at the same time, diminishes the toxicity of both. Thus, knowing the urinary poisons and their various sources, he has been enabled to study that form of intoxication which is due to their retention, and known as uræmia. Whilst carefully keeping

clear of the urotoxic accidents liable to intrude themselves and complicate matters in disease of the kidneys, such as albuminuria, arterial œdemas, including, for example, that of the brain. By this means he has obtained decided proofs of the fact of the reality of toxic uræmia, while showing that the urine is not toxic. He shows that the uræmic urines are not toxic, for the reason that all the toxic substances which the urine normally eliminates are found to be retained in the organisms of those affected. To the question : "Is all that is retained toxic, or is only a portion of it, and, if so, which portion?" he finds it is neither the urea nor the potash exclusively. Neither of these of itself explains the intoxication. Each of them contributes in part, though differently, to that condition as a whole; the colouring matters three-tenths, the extractive matter one to two-tenths, potass and mineral matters four to five-tenths. A knowledge of the multiplicity of the toxic agents enables us to understand, according as one or other of these eliminates, the various clinical forms uræmic poisonings may assume, the convulsive or comatose in particular. The presence of certain special symptoms, such as hypothermia, contraction of the pupil, and pathological intoxications, which he endeavours

to show, not only satisfy scientific curiosity, but are suggestive of practical application and have a therapeutic value.

Next he proceeds to examine the morbid conditions which are caused by gastric embarrassments, of which excessive accumulations, constipation, and intestinal obstructions are examples. He traces the history of a variety of intoxications of intestinal origin, citing that of Senator, in which the offending element was sulphohydric acid. Poisoning from fish, which he personally observed, and in which the presence of an excess of alkaloidal substances, to which the same might be charged, was present, and refers to the instance of over-kept stuffed goose, in which Brouardel and Boutmy succeeded in isolating toxic alkaloids, showing that all these cases had actually passed through infection to intoxication. There was detected between the ingestion of the putrid aliments and the setting in of toxic symptoms a period of incubation. It appeared to him that the poison, elaborated by microbic action of the goose meat, was too small in quantity to induce poisoning, but the microbic putrefaction acquiring a greater intensity in the intestinal canal became much increased, and then the toxic products were sufficiently abundant to produce

intoxication. Here, again, incubation compels us to admit infection ; but that the infectious agents manufacture a poison, and infection results in intoxication. Bouchard holds that the usual circumstances under which such accidents of toxicity take place, in consequence of the formation of poisonous elements in the digestive tube, is in the singular condition he recognises as dilatation of the stomach, and which—apart from dyspeptic troubles as nervous derangements always acknowledged in the *cortége* of dyspeptic disorders—seems to him to be capable of setting up many other disorders, such as albuminuria, a condition usually chronic, and liable to become permanent, but amenable to treatment, and that successfully when the real cause has been discerned. It is by setting up anomalous gastic fermentations, which extending to the intestinal canal, give rise to the formation of poisons, particularly acetic acid, that dilatation of the stomach vitiates nutrition of various structural tissues, even of the bones and cartilages, and may not be a stranger to ostiomalacia, nodular rheumatism, perhaps including rickets. Of other maladies dependent on matured intoxications caused by dilatation of the stomach, he thinks the most manifest are chlorosis and pulmonary phthisis.

This may take some by surprise. It is, however, dealt with in a most exhaustive manner by the learned experimentalist, who, if he does not convince, at least makes it very probable that dyspeptic and gastric affections must henceforth be given a wider range in pathological research. It may be difficult to accept the lengthened list of maladies dilatation of the stomach is parented with. Still it must be owned that it is precisely with respect to this question of etiology that we are most ignorant, and any rational examinations of it based on demonstrated fact ought not to be lightly estimated, thus indicating the *rôle* which secondary or indirect poisoning plays, even in infectious maladies. Bouchard proceeds to lay down his views regarding the treatment of typhoid fever in which he sees chiefly indicated intestinal antisepsis, and general balnear anti-thermics, and a particular line of dietary, thus laying down, *apropos* of enteric fever, general rules which might be found applicable to other acute maladies.

He next goes on to show that part intoxication holds in jaundice, pointing out that here intoxication is twofold. The bile, contrary to to what has been hitherto supposed, is toxic, particularly in its colouring matter, and that

what protects the organism from the action of this element is the urine, which eliminates incessantly one part of it ; there is also the cellular tissue, the white fibres of the fibrous tissues of which, fix or take up colouring matter not eliminated, and which, should it remain in the circulation, would seriously affect the functional play of the nerve cells. As for the other part, the biliary salts, they go to augment disassimilations, to destroy the muscular cells and blood globules, thus liberating the poisons, organic and mineral, particularly potash.

In maladies that give rise to jaundice, the liver, which is normally charged with the protection of the organism from intestinal poisoning, is deranged or obstructed in its functional action. It ceases to fulfil its part ; it ceases to manufacture urea—the diuretic *par excellence.* It is the urea, which, by forcing the renal barriers, conveys with it the other toxic materials. By its means a complex process takes place of intoxication, whose successive phases are cholæmia, acholia, and uræmia. There consequently can be but little question that the safeguard of the organism from intoxication lies chiefly in the kidneys. So long as this organ is functionally active, the urines of jaundiced subjects are very

toxic, not from the bile which they contain, but from the material resulting from the unusual and increased disassimilation. When the kidneys cease to discharge their function of depuration, the urine of the jaundiced patient ceases to be toxic ; and the patient becomes poisoned from the retention in the system of the poisons that failed of a normal discharge.

But the normal poisons are not alone in question in all intoxications. Bouchard points out in the acute atrophy of the liver the presence of a singular substance produced by the organism, which elaborates vitiated material, and further points out unusual albumen, unusual transformation of medical agents, such as naphthalin, which ceases, in the case of hypatic atrophy, to be eliminated in the state of naphthy-salphite of soda ; some of these are toxic. Again, we are reminded that in glycosuric patients, besides accidents resulting from the complete destruction of sugar formed by the organism, this body may give rise to substances which, in the urines of subjects suffering from diabetic coma, take a wine red colour in contact with perchlorate of iron. These substances, however, are not alone met with in the diabetic, for they have been detected in the cases of dyspeptic coma, in certain cases of cancer of the stomach, and

permanent anuræia, leucocythæmia, and more recently Bouchard has met with them in typhoid fever. These substances, as experimentally proved, are toxic. Contrary for the most part to the auto-intoxications hitherto exposed, that called acetonæmia is an intoxication by an anomalous poison, a morbid poison.

In cholera, also, there is sometimes the formation of anomalous material, and some of these are obviously alkaloidal ; this is detected by the violet colour given by the urines of cholera patients, even on emission, while under naphthalin medication. But cholera is an example of multiple intoxication, and Bouchard has shown that in choleraics there is present a special poison, practically unknown, elaborated by the organisms. This substance appeared to Bouchard to be clearly evidenced from the specific toxicity of the urines of choleraic subjects when injected into the veins of rabbits ; they determined in definite symptoms characteristic of cholera, though not the malady itself. He has also pointed out that, besides the accidents which choleraic intoxication exhibits the persons attacked are subject to secondary intoxication consequent upon suppression of urine. This is from the retention of the normal poisons. Myosis—pupilar con-

traction—is present as the clinical criterion of uræmic intoxication having taken place.

Bouchard's admirable course on auto-intoxication closes with therapeutical applications deduced from the pathological conception which the study imposes. The treatment of auto-intoxication draws largely on the antiseptic method ; and we naturally wish to know what may legitimately be expected of antisepsis in general. We know that the mastery of the mechanism of maladies does not bear with it the mastery of the remedy, but from the lucid exposition on this head, good results, if limited, may be reasonably looked for.

Auto-Intoxication In Health.

PART V.

THE periodical suspension of the activity of the superior nerve-centres is the dominant character of sleep. The attempt to explain it by the condition of the cerebral circulation has often been made ; but, by a singular contradiction, some authors set up the intervention of congestion, whilst others insist on anæmia. Recent researches seem decidedly favourable to this latter hypothesis however, in support of which somnolence from great loss of blood, and that kind of sleep that Fleming was able to produce by the compression of the carotids may be cited. The variations of the cerebral circulation present then a certain relation with the alternations of sleep and wakefulness, but as these variations themselves require explanation, they do not suffice for any theory of sleep. The capital importance of oxygen in keeping up the activity of the tissues once recognised, it was very natural to make it play a part in the explanation of sleep, and to attribute it to a less absorption of oxygen—to

an anoxia of the brain. This is an idea which goes back to Alexander von Humboldt, at the end of the last century, and which has been since maintained with certain variations by Purkinje, Pfluger, and others ; but this affords no explanation of the cause of the periodicity of normal sleep. Why should the quantity of oxygen received by the brain diminish at certain times and increase at others ?

Sleep is not the only phenomenon which returns regularly and in some sort rhythmically in the life of the organism. The movements of respiration and the contractions of the heart are in point. The study of them ought to simplify the problem.

It is generally admitted, thanks to the labours of Rosenthal, that the respiratory system is essentially regulated by the richness of the arterial blood in oxygen and carbonic acid. When the blood is charged with oxygen, the nerve-centre which governs respiration, suspending its activity, the tissues take up the oxygen of the blood, replace it by carbonic acid, and thus the blood, becoming modified, excites the respiratory centre. A respiratory movement is then produced, the provision of oxygen is renewed, the carbonic acid eliminates itself ; things restored to their initial condition,

the process recommences. It is instability, even in the condition of the blood, which excites the movements necessary to recovery of the primary equilibrium.

The exhaustion of a muscle by labour, and the restoration of its excitability by rest, are phenomena still more comparable with the sensation of fatigue and the restorative effects of sleep. The researches of J. Ranke, which date more than twenty years back, tend to the admission that the exhaustion of the muscle results from the accumulation of substances produced by its contraction, in particular that of lactic acid. If we inject these fatigue substances, as Ranke calls them, into a fresh muscle, it becomes incapable of working—it is exhausted ; if we remove them by an artificial washing, or if we allow the circulation of the blood time to carry them away and to replace them by other materials, the fatigue disappears, the muscle acquires again its contractility, it renews itself. Ranke supposed that fatigue substances operate by monopolising the oxygen to the detriment of the muscle. In any case it would here be still the instability in the chemical condition of the organ—its temporary intoxication—which forces it into a state of rest, until it be disencumbered of the products

of its activity, and finds itself in some sort changed.

To M. Leo Errera, of Belgium, we are indebted for one of the most interesting contributions to this subject. Well known for researches in connection with the alkaloids of plants, this accomplished teacher has recently directed attention to those of animals in explanation of the physiological conditions of fatigue and more particularly sleep.

To the questions involved, and still awaiting solution, the best informed, as Exner and Beaunis, had declared that we know nothing definitely on the subject. More recently, however, new facts have come to light which materially alter the position ; in both conditions the principal phenomena, at least, may shortly cease to be a mystery. With M. Errera's work before us, let us see how far this is probable.

I.

The Animal Alkaloids: Their probable Role in Fatigue and Sleep.

M. Errera in his remarkable paper entitled "Why sleep, and How?" of which the following is a *résumé*, enters on the subject by asking whether a theory of toxicity, analogous to those of respiration and of muscular fatigue, would not apply to sleep. Heynsius and Durham have assented to this view; since Obersteiner and Binz also declare in the same sense. These latter think that the products of exhaustion are continually forming within the brain when active; that their accumulation brings on sleep; and that they are then eliminated by the blood which passes through that organ. But what are those products? From what we know of the reaction of the grey substance and tetanised nerves, Obersteiner was of opinion that it operated essentially as

an acid ; and such also was the opinion of Heynsius and Durham, and of Binz. Preyer has expanded this idea, and ingeniously combined it with the theory of sleep by default of oxygen. He arrives also at a conception altogether parallel to that which Ranke had formulated for the muscles. According to Preyer all organic activity gives rise to products of exhaustion, to substances which he calls *ponogenes*—from πόνος —labour, and λένεοις—origin—which accumulate during wakefulness, and, being very oxidisable, terminate by diverting to their profit the oxygen destined to keep up the activity of the different glands, muscles and brain, in such a fashion as that the mental acts and voluntary movements are depressed ; and cause the organism to fall asleep.

Among the ponogenic substances it is to lactic acid that Preyer ascribes the principal part, and he has made the attempt to demonstrate experimentally that this product entering into the organism induces sleep. These experiments have been repeated in different ways. Unfortunately, as Preyer himself has recognised, the results are not constant, either in the case of man or of animals ; thus the theory has not been generally adopted by physiologists.

At the time that Obersteiner, Binz and

Preyer made known their ideas, we knew of no product of the animal organism similar to the somniferous alkaloids of certain plants. Recent researches have shewn that such do exist, and the question of sleep now naturally presents itself under quite a new aspect.

Extending to animals, alive and healthy, the researches which Selmi had made on the dead body, Armand Gautier has succeeded in extracting from the flesh of mammifera—beef—a series of five organic bases more or less akin to creatin : creatinine, xanthine, &c. He designates them under the name of leucomaines, so as to recall the fact that they are analogous to the cadaveric bases or ptomaines. Pouchet and Bouchard found the alkaloids in the urine of human beings. Gautier himself had indicated it in their saliva in its normal state, and he concluded that animals normally produce alkaloids after the fashion of vegetables. What are the physiological actions of these leucomaines? The aqueous extract of the saliva "is poisonous or narcotic, at least for small birds ;" next as to alkaloids from muscular juice, Gautier speaks of them as endowed with an action more or less powerful on the nerve centres, producing somnolence, fatigue, and sometimes vomiting and purging. There is

here clearly a question of substances fatiguing and somniferous, such, in one word, as the toxic theory of sleep requires them to be. Curiously, the memoirs of Gautier and their subsequent discussion at the Académie de Médecine, where the importance of leucomaines as regards pathology has been so clearly brought into relief, their signification physiologically seems to have been almost overlooked, and their probable relation to sleep has not, so far as I know, been mentioned. What could be more natural than to bring together the work of Gautier with those above mentioned? The idea was in the air, and was incidentally alluded to by De Parville in a scientific article of the *Journal des Débats*. The writer in stating the results that Gautier had just obtained, quotes from him this phrase: "It is after perfect sleep or rest that the animal is more particularly anærobic and consumes more oxygen than it receives," and he adds, in a note, "during sleep the oxygen absorbed does not correspond to the carbonic acid exhaled. We should be tempted to believe that the excess burns the toxic matters, and that sleep would principally be caused by the accumulation in the blood of leucomaines or analogous substances." It is to be observed

that the accumulation of oxygen during sleep, on which De Parville insists, seems to be disproved. Voit expresses himself thus on this subject: "It was in consequence of error in the mode of conducting the experiment that Pettenkofer and myself had concluded at the time that the oxygen is stored up in considerable quantity during the night, and utilised afterwards in the daytime and during labour."

Quite recently Bouchard, in his researches on the toxicity of the urine of a healthy human being, has compared the urine secreted during wakefulness and during sleep, and, in so doing he makes passing allusion to the theory of sleep. Without specifying the nature of the poisons with which the question has to do, he says: "The urines of waking and sleeping not only present differences in intensity, they differ also as to quantity. The urines of the sleeping hours are convulsivant, the urines of the waking hours are very little so or not at all; but they are narcotic." It is at this stage that one might ask whether Preyer's toxic theory of sleep should not be accepted. What is certain is, that during wakefulness the body fabricates a substance, which if accumulated would produce sleep; and that during sleep it elaborates in

place of this narcotic substance, a convulsivant, which if accumulated, would produce the muscular shock which is provocative of waking. It perhaps might be objected that if the poison which is narcotic brings on sleep by its accumulation in the organism, it is in the tissues and not in the urine that one ought to meet with it during wakefulness. But to express oneself on this point safely, as on many others, it will be well to await the continuation of the labours of Bouchard, and notably the extraction and the dosage of toxic substances. In any case, it appears rational to base a theory of sleep on the products that may be detected in the tissues of the organism itself rather than upon those which it eliminates by its secretions.

According to a profound remark of Claude Bernard, all vital manifestation is connected with the destruction of organic matter. This is a consequence of the great principle of the conservation of force. When a muscle contracts, when a nerve feels, when a brain thinks, it is at the expense of organic substance; there is a corresponding destruction and consumption of elementary material. In a certain sense life is thus but a prolonged partial suicide, to adopt an expression which Peter recently made use of.

If it be a commonplace to say that to labour, the living being must burn organic matter as the steam engine burns coke or coal, it is clear that in the one case as in the other, waste, ashes, and ponogenes ought incessantly to be produced. No more in the living than in the artificial machine can these ashes accumulate without inconvenience, as they tend to the detriment of the tissues by engrossing the space which the new utilised elements ought to occupy. But there is more than this, the cellular scoriæ are probably injurious in another way. Besides positively encumbering, they may in their turn react upon the vital phenomena.

We have no difficulty, then, in conceiving that the animal machine cannot continue to work if it does not disencumber itself of its waste,—its ashes,—and if it does not procure fresh combustible matter; the elimination of ponogenes and organic reparation appear to us as the inevitable necessities of work. It is possible, especially when the activity is intense, that these two functions may be accomplished less quickly than the inverse phenomena. The organism will then be at the end of a certain time impaired by its overwaste, and find itself incapable of continuing to work until it can

be purified and reinvigorated by rest. And here, to begin with one cause of alternations more or less regular, we foresee that phases of activity and repose must necessarily in turn succeed each other. It is, moreover, no other than a manifestation of the character which discovers itself in all movement : rhythm.

But if general considerations permit us to understand the necessity of repose, they are insufficient to explain to us the mechanism of sleep. This phenomenon signifies something more than the functional incapacity. It is eminently a question of a nervous order. All cellular waste, every ponogenic body is not actively somniferous. It requires for that : firstly, that this body should operate in a special manner upon the superior nerve cells ; secondly, that it should suspend this activity for a time.

Now, do we know any substances possessing these properties ? Undoubtedly ; ether, chloroform, hydrate of chloral, and in an eminent degree the alkaloids which are narcotic ; morphia, narcein, &c. And if we now pass in review the products fabricated by the organism, there is certainly none of them which will better satisfy us than the leucomaines under the conditions which we have just theoretically indicated.

The study of the leucomaines is scarcely as yet begun, but an analogy which seems interesting becomes evident even now. According to Gautier, the greater part of the leucomaines, as well as of the ptomaines are very oxidizable, and morphia is precisely that which makes itself observed by reason of its great oxidizability. Bettink and Van Dissel assure us also, that out of forty-two vegetable alkaloids tested by them, morphia alone divides with the ptomaines the property of forming Prussian blue, by reduction of the perchloride of iron and ferricyanide, and that notwithstanding the presence of an oxidizer so powerful as chromic anhydride.

It may be asked, in what way do leucomaines act upon the nerve cells. Is it directly or indirectly in the taking up of oxygen, as Preyer supposed, in regard to his ponogenes? It would be premature to wish to settle the question definitely, but in the actual state of investigation the first hypothesis appears much the more probable. If we take as terms of comparison the vegetable alkaloids, no one will be likely to suppose that morphia brings on sleep by the subtraction of oxygen; for one centigramme of a salt of morphia, a sufficient quantity of itself to cause sleep, does not require for its

complete oxidation more than two centigrammes of oxygen—say, less than the eightieth of what we inhale every minute. Again, we do not know what quantity of each leucomaine is necessary to occasion fatigue and somnolence, of which Gautier speaks, but the quantity is certainly small. The moment, moreover, one comes to think how little abundant the leucomaines are in the normal organism, it becomes difficult, if not impossible, to attribute sleep to the privation of oxygen, which may result from their oxidation. Another fact also makes against the theory of sleep by anoxia, it is that many oxidizers—halogenium, ozone, oxygenised water — are narcotic. There are, on the contrary, good reasons in favour of a direct action of leucomaines on the brain. Rossbach has seen that many vegetable alkaloids, morphia, quinine, atropia, veratria, strychnine, modify the albuminoidal matters, such as the white of egg, the serum of the blood, the muscular juice, and that by augumenting their coagulability, the albuminoidal precipitate thus obtained preserves always a certain quantity of alkaloid even after prolonged washing. This precipitate exercises no coagulating action upon the white of egg when dissolved, and Rossbach

thence concludes that the alkaloids must be in chemical combination with the precipitated albuminoid material. Binz tells us that soporifics, such as morphia, chloral, chloroform, and ether put into contact with the grey substance, renders it turbid. This is the sign of a species of coagulation which other non-soporific bodies would not occasion: atropine, caseine, chlorox-alethylin, camphor, pyrogallic acid. Claude Bernard was also of opinion, at least as regards ether, that anæsthesia is caused by a sort of coagulation. Let us observe that muscular fatigue could no longer be attributed, as Ranke thought, to a monopolising of the oxygen by the products of contraction, but much rather to a direct influence of the acids formed; for the phosphate acid of soda, which is not oxidizable, absolutely "fatigues" the muscle just as lactic acid does. Leucomaines might, again, act indirectly in another manner by modifying the cerebral circulation. It is a hypothesis which has already been put forward to explain the action of narcotics, and in this way the vaso-motor theory of sleep is arrived at. But such opinion seems contradicted by the direct observations of Binz. In the dog and rabbit when trepanned, he saw that anæmia of the cerebral surface only supervened slowly in the

complete state of sleep. "Anæmia is then in this case a consequence of sleep, and not sleep the consequence of anæmia." The author adds, after instancing the case of the alimentary canal, which is pale and bloodless during a state of fasting, and filled abundantly with blood during digestion: "Cerebral anæmia in prolonged narcosis is in harmony with this general rule, that the flow of blood towards the organs diminishes when they are at rest."

The influence of ponogenes may then probably be summed up in these terms: not anoxia, not anæmia, but direct intoxication. A theory of sleep ought to account for the normal linking together of these three things: work, fatigue, and sleep. It is easy to see that the toxic theory satisfies this condition. All work, whether it be muscular or cerebral, engenders loss of material. This deterioration renders the continuation of labour painful: this is fatigue. Finally, the waste *débris*, and notably the leucomaines, finish by intoxicating the superior nerve centres—as morphia would do—to the extent of inaction: this is sleep. Here we have the phenomena reduced to their most simple expression. But a mass of accessory circumstances arise to complicate the consideration of the question. The most important it

is necessary to note. First of all, the living being struggles incessantly against the intoxication by which it is menaced. It seeks to disencumber itself of its refuse material; the circulation drains them off and expels them by respiration and secretions; the liver, it seems, arrests or destroys one portion of them. The more intense any labour is the more do all these functions become active: the circulation increases, washing and cleansing the organs; the respiration accelerated, eliminates more carbonic acid; the emission of urine is often augmented; perspiration makes its appearance, refreshing the organism, and taking away from it, moreover, a considerable quantity of refuse products, such as urea and creatin. These multiple depurations enable the organism to maintain activity for a certain time, but not indefinitely. Why so?

If, by an excess of work, certain of our organs have consumed all their utilizable materials, and thus grow encumbered by ponogenes, it is clear that they are, until a new order of things succeeds, incapable of further work. But we do not arrive under ordinary conditions at this extreme degree of exhaustion; it is even doubtful whether we ever do arrive at it. It is a fact that the sensation of fatigue has

already become invincible, before the physical, the real fatigue, has attained its ultimate or extreme limits. The ponogenes operate, not only upon these organs where they have begun their existence, but even upon the nervous extremities which border on these organs and upon the centre themselves. To this triple influence of the ponogenes three significations of the word "fatigue" correspond. In effect, there is room to distinguish between the true fatigue of the muscular fibres of the arm, for example, which is measured by the diminution of their excitability, the fatigue which is subjective, which we feel locally in this arm; and the general sensation of fatigue lassitude which explains itself by the desire of sleeping. After having lifted for some time a weight, we may experience an intense fatigue in the arm, but no need of sleep, whilst we may fall, as they say, asleep, without experiencing any considerable local fatigue. Of these two sensations, one is peripheric, the other is central. It is this latter which interests us the most, and it is its genesis that it behoves us to study most clearly.

Cerebral activity, such as manifests itself during the state of wakefulness, is connected with reactions of a chemical nature, with discharges which occur in this eminently explosive

matter of the protoplasm of the nerve-cells, and the gray cortex. Now, among the ponogenes constantly engendered within the different organs which are in operation, we know that there are narcotic compounds, comparable to alkaloids. In all probability these bodies have a particular affinity for the nervous corticle cellule; in any case they act upon it, they modify it, they fix themselves there more or less steadfastly. Their elimination by the emunctories, as already mentioned, will never be other than partial; whilst one portion will be drained by the secretions, another will possibly be undergoing destruction by oxidation, a third will be retained within the brain. It is believed that the nerve centres, thus modified, perform with less and less facility their function of explosion, and it will require excitements more and more vigorous to maintain the condition of wakefulness; after a certain stage our movements become tardy, our sensations become blunted, our thoughts are clogged—in a word, we feel ourselves fatigued. There comes at length a moment in which the ordinary excitements are no longer sufficient to permit the explosion of the cerebral protoplasm; its activity is provisionally suspended; we sleep. By this theory, it is obvious that the ponogenes

only operate on those of the nerve-cells into which they penetrate. This localised action explains to us what we may call "partial slumbers." The profoundest sleep, says Exner, with reason, is connected by insensible transitions with perfect wakefulness. If one is observant whilst falling asleep, it may be remarked that the circle of ideas with which one is occupied becomes more and more contracted. We can say that certain groups of ideas are still wakeful, whilst others are already subject to sleep. The cells of the organism fall asleep one by one, even as they die one by one, following a hierarchical order. Whilst admitting a great latitude for the intervention of accessory causes, we foresee, nevertheless, that the most elevated of the centres are in general the first to become drowsy, then sleep overtakes by degrees the inferior centres.

These remarks explain in a certain measure the phenomena of somnambulism; for Jean Müller has already shown that the question there is one of partial sleep. On the other hand, certain superior centres the first asleep, are capable of awaking themselves separately or in groups. Perhaps one may come by this means to understand the variety and the want of connection in dreams, and painful night-

mares, during which we endeavour to perform a movement, and feel ourselves restrained; here the motor centres would be asleep, whilst certain intellectual centres would be awake. In somnambulism, on the contrary, it would be the motive centres which were awakened, and the intellectual centres that continued asleep. Contrary to Preyer, Errera is led to regard the somniferous action of the ponogenes as direct, and not as the indirect result of a subtraction of oxygen. The reasons have been stated. However, the oxidizability of the leucomaines, in place of being the cause of sleep, explains according to our view the cessation of it.

If the accumulation of a certain quantity of leucomaines within the ganglionary cells brings on fatigue, then sleep, the sound awaking and refreshed feeling which accompanies it, must be due to the disappearance of the leucomaines. Have they been simply removed by the circulation, or are they destroyed? Both factors might intervene, but since it is probable that the leucomaines are chemically retained in the cerebral nerves, as were the alkaloids in the experiments of Rossbach, the mere blood-washing would not remove them except with difficulty; and since from other sources we have a knowledge

that they are oxidizable, it is natural to think that the oxygen whose oxidizing power still is being exercised in the living organism, attacks them and burns them little by little. Does this only take place during sleep? There is no reason for thinking so. The accumulations of leucomanies during the state of wakefulness does not prove that their production is suspended. It signifies only that the production is then in excess of the oxidation and elimination united, which is only very plausible. During the condition of waking, the activity of the organs continually engenders new quantities of them ; during sleep the production is, at least very much reduced, for the muscles are then in repose, the pulsation has become lessened, many secretions and respiration are diminished, the brain is out of gear. Now, the normal adult requires as near as may be about eight hours of sleep as against sixteen of waking, so we may conclude that the ponogenes are formed on an average, during waking, one and a half sooner than they oxidize and eliminate themselves. It is useless to adduce that here a mass of factors are overlooked, and that this figure represents only a crude approximation. As there is no reason to admit that the products of oxidation of the leucomaines can have, like

them, a special affinity for the protoplasm of the gray substance, we conceive their being immediately swept away in the circulatory current. The nerve-cell, therefore, is cleansed, it becomes again accessible to impressions from without, and a slight exciting cause suffices to bring about waking. But this is not the whole. Sleep does not consist alone in the elimination of ponogenic matter. That is only one phase of things, and we have already said that we must regard also the organic reparation. Side by side with the cleansing there is the reparation. When once the leucomaines have invaded and paralysed the cortical cells, all the organism is relieved of the tyranny of the brain, and each tissue is capable of restoring itself tranquilly by inmost nutrition. Thus we understand that man rises up in the morning, not only freed from his fatigue, but armed with new strength for a fresh activity, and that sleep, even when artificial, may be of benefit. As regards the amount, the quantity of leucomaines contained in the organism is doubtless subject to continual variation; it increases or lessens according as the productive phenomena or the disassimilation preponderate. We see, thus, that an increase of work may be capable of leading to a decrease of fatigue, if this work

increases at the same time and in a stronger proportion, the oxidation and expulsion of waste. Perhaps in this we reach one of the causes why exercise in the open air is so healthy. At other times the decrease of fatigue is only apparent. In proportion as an excessive weariness takes hold upon the body, and as the cells which intervene in conscious perception are finally exhausted in their turn, consciousness becomes more and more obscure, and fatigue, in so far as regards the sensation experienced by the patient, may thus diminish, because of the very excess of work. It may happen, from an opposite cause, that the beginning of rest, far from resting us, augments the subjective fatigue. But this kind of phenomenon requires another explanation, about which we shall say a few words.

In the present day it will scarcely be doubted that certain chemical decompositions of the molecules of the nervous protoplasm are the condition of cerebral activity. From all that precedes we are led to attribute sleep also to a chemical reaction between this protoplasm and the leucomaines. Now, in virtue of principles of mechanics, it is in general more difficult to impress on a body a determinate form of vibrations when it is already vibrating than when at rest.

Without quitting the domain of physiological chemistry, Nageli has shown that the existence of fermentation hinders more or less completely a different fermentation from establishing itself in the same medium. If we apply the like idea to the ganglionary cells, a mass of facts which are familiar to us become at once intelligible. In normal life we are conscious of no fatigue during the greater portion of the day, because the cerebral protoplasm defends itself against the ponogenes by its very activity, and it is only towards evening, when the army of the ponogenes is become more formidable, that the nerve centres commence to become feeble. One may up to a certain point struggle against fatigue, or betake oneself to repose; the vigorous and varied sort of excitements retard sleep, whilst tranquillity, monotony, inaction, *ennui*, and silence are favourable to it. Immediately that the nerve-cells give way before the enemy, they lessen their activity, the leucomaines invade them with more and more facility; first fatigue, then sleep, supervenes. Fatigue appears to us, from this point of view, like a conflict between the activity of the protoplasm and the invasion of the waste matter; and sleep is the temporary victory of the waste matter over the protoplasm.

These observations give the key to a phenomenon that, at first sight, might seem to be opposed to our theory, which is this:—Although the formation of narcotic substances goes on all day, the passage from wakefulness to sleep is usually rapid enough. Our day of work has but little twilight.

This leads to a delicate question, and one which as yet has been very little studied—the soundness of sleep. Let us try to enter upon it. According to Errera's theory the soundness of sleep must be at all times in proportion to the number of the molecules of the cortical centres, which are in combination with the leucomaines. At the beginning of sleep, everything facilitates the arrival of the leucomaines; they are relatively in abundance in the organism, and the central cells being inactive, leaves them free to numb them. Thus sleep becomes soon more and more profound, till the maximum is attained, when all the stock of leucomaines combines. But during this time the destruction and the elimination of leucomaines have continued going on more actively in proportion as the gray substance appeared to be a favourable medium of oxidation; a portion then of the leucomaines will be constantly destroyed within the brain, and the intensity of the sleep will not

take long to decrease, but that with a decreasing rapidity, seeing that oxidation takes place on less and still less quantities of leucomaines.

Experiment agrees very satisfactorily with these deductions. Kohlschutter determined, from half-hour to half-hour, the soundness of sleep in the case of the same individual, according to the intensity of sound necessary to excite awakening. In spite of the sources of error in a similar proceeding, the following results might, according to Exner, be regarded as established. The intensity of sleep increases promptly during the first hour; it then decreases, at first rather rapidly, and then more and more slowly until awakening is complete. Kohlschutter has given us a curve which indicates these variations; a thing of some interest, and, as we may foresee, the form of this curve remains the same, whatever may be the intensity of the sleep absolutely. It applies as well to sleep produced by a slight degree of alcoholic intoxication as to normal sleep. In forming a suitable hypothesis as to the proportion of leucomaines which are being continually oxidized, Errera's theory would furnish a curve of the same kind. An observation of Brever, which it is easy for one to repeat on himself, deserves here to be mentioned. We often go to sleep whilst pass-

ing through oscillations of consciousness and of unconsciousness more or less distinct. The fact seems sufficiently explicable. At the precise moment at which we lose consciousness of what surrounds us, the least diminution in the flow of the leucomaines towards the brain may permit the protoplasm to escape sufficiently their action for consciousness to return ; but, the flow again augmented, consciousness vanishes anew, and so continues until the reign of sleep is definitely established.

If this theory of sleep is correct, it may be asked whether there may not be counter-poisons, antidotes of our ponogenes which are soporific —ponolytes, if you will—which might counteract the fatiguing action of the products of activity. Why not? Grutzner and Gscheidlen have established that reducing substances are formed in the muscle by the effect of contraction ; and reciprocally, it appears, according to Kronecker, that oxidizers, such as the permanganate of potash, in very feeble solution, restores to the fatigued muscle its excitability and strength. We likewise know that the leucomaines are oxidisable, and it is probable that one might destroy them by means of oxidizers. Yawning, that deep inspiration of the tired man—might its purpose not be that of

furnishing him with a precise increase of oxygen? But, besides the oxidizers, might it not be possible to discover veritable antidotes to the narcotic leucomaines? For example, alkaloids antagonistic to these substances, as atropine is antagonistic to pilocarpine; coffee, which wakes up the brain; coca, which suppresses, they say, for several days together, hunger and fatigue, are perhaps of the number. We must frankly add, however, that if a pharmaceutic product happen to obviate fatigue artificially, that does not imply that it procures by the same time organic restoration—the restorative effect of a good sleep.

It would be well, however, to guard against explaining too many things by alkaloids; as M. Guerin has remarked, "having abused the microbes we must endeavour to avoid abusing the ptomaines." But it is just to observe that if Selmi has seen all the importance of animals alkaloids, as regards forensic medicine, if Gautier, Bouchard, and others have indicated their *rôle* in the genesis of diseases, their important place in normal physiology still remains, to a larger extent, a virgin study, and one which promises fresh harvests in discovery. Already we catch a sort of glimpse that inebriation from work, inebriation from success, inebriation from

love, might well cease to be mere metaphors, and range themselves with the actions of different toxicants upon our nerve centres. Errera hopes to have shown the probability that fatigue is, in the proper sense of the word, an intoxication, of which sleep is the normal antidote. Who knows whether many physiological acts—respiration, movements of the heart, micturition, defæcation—may not be like sleep dependent on specific bodies, acting, be it on the nerve-centres or upon the peripheral organs? Organic rhythm would be due to the fact that a given physiological act gave rise to substances, which tend to provoke the contrary act, just as the descent of the pendulum provides the necessary power to cause it to rise again. A very recent work by Zuntz and Geppert concludes that over and above the holder of the blood in oxygen and in carbonic acid, there is yet a particular and unknown substance produced, and chiefly by the muscular activity, which normally intervenes to regulate the respiratory movements.

Errera, in conclusion, sums up the theory of sleep in a few lines: "The activity of all the tissues and, in the first line, of the two most active, the nervous and the muscular, give rise to bodies more or less analogous to alka-

loids, the leucomaines. These leucomaines are productive of fatigue, and are narcotic. These leucomaines, then, must necessarily occasion fatigue, and bring on sleep. In awaking, if the organism be thoroughly refreshed, it is because these bodies have disappeared ; because in such case, they are destroyed and eliminated during normal sleep, the restorer." All this appears logically indisputable ; but it pertains to direct experiment to furnish the proofs where we as yet have only arguments. The quantity of leucomaines, their presence in the brain, the more complete study of their physiological properties are the first problems which offer themselves for solution.

It may be asked whether the leucomaines of Gautier have so close an affinity to the ptomaines and the alkaloids, properly so-called, as that author asserts. There is here a question of degree which admits of difference of opinion. What appears to be established by his researches, is the very general formation of organic alkaloids in living beings, many of which possess narcotic properties. Here we have all that is necessary to serve as a starting-point for the toxic theory of sleep such as M. Errera has so ably brought before our notice.

APPENDIX.

APPENDIX.

INTRODUCTION BY PROF. ARMAND GAUTIER,

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(FRENCH TEXT.)

LES phénomènes intimes qui se passent dans les cellules vivantes, végétales ou animales, sont encore trop peu connus dans leurs mécanismes, et même dans leurs effets, pour qu'on puisse essayer de déterminer les causes profondes de leur évolution normale ou anormale d'ou résultent la santé ou la maladie. Mais ce qu'il est possible d'affirmer nettement c'est que ces phénomènes sont tous physico-chimiques, et que si la raison de leur succession nous échappe encore, ils ne sauraient ne point obeir à cette loi naturelle tout à fait générale qui veut que l'energie sous toutes ses formes,—chaleur, travail musculaire, action chimique ou nerveuse, &c.,—résulte d'une transformation de l'energie méchanique, potentielle ou actuelle, préalablement contenue dans la matière de chaque cellule.

Or l'on sait aujourd'hui que chez les êtres vivants, comme dans les substances inertes, les modifications qui rendent l'energie sensible et utilisable sont de deux sortes. Dans un premier cas, elle résulte des modifications moléculaires produites dans la matière sans intervention de l'oxygène. Les organismes qui empruntent entièrement leur energie a cette

source intérieure sont ceux que M. Pasteur a nommés *anaerobies ;* ce sont généralement des ferments inférieurs ; mais j'ai montré ailleurs, que contrairement à ce qu'on supposait *a priori* la vie des grands animaux est pour un large part, le cinquième environ, *anaerobic.* La seconde source de l'energie résulte de la combinaison des substances chimiques et particulierement, pour celles qui sont combustibles, de leur union à l'oxygène. Les êtres qui empruntent surtout leur energie aux combustions internes sont les *aerobies.* Il en est de végétaux, mails ils appartiennent généralement au règne animal. Ils absorbent l'oxygène, brullent les matériaux de leurs cellules, rejettent incessament l'acide carbonique, l'eau, l'urée . . . et corrélativement bénéficient de l'energie qui résulte de ces combustions.

Dans les deux cas, les produits de la vie deviennent impropres à entretenir les fonctions de la cellule qui les a formés ; ils doivent disparaitre. L'animal succomberait rapidement si l'acide carbonique, l'urée, l'eau, et même la chaleur qu'il forme sans cesse, s'accumulaient dans son organisme. Mais dans le cas de la vie anaerobie les produits qui se fabriquent, sans intervention d'oxygène, surtout ceux qui derivent du dédoublement des matières albuminoides, sont particulierement dangereux. Ils sont de la nature de ces substances qui se produisent dans toute fermentation bactérienne putride. L'on verra dans la Première Partie de cet ouvrage que cette vie bacterienne anaerobie, donne lieu (outre d'autres corps trés vénéneux) à des alcaloïdes, rencontrés aussi dans

les matières cadaveriques, et qui portent pour cette cause le nom de *ptomaines.* Ceux de ces corps qui sont constants dans toute fermentation putride prolongée appartiennent aux series pyridiques et hydropyridiques ; ils ne sont pas éloignés des bases vénéneuses de la ciguë et du tabac. On a depuis démontré dans les produits de fermentations plus recentes la présence de substances alcaloïdiques plus puissantes encore, telles que la muscarine, le poison de la fausse-oronge, &c. Si donc, comme je l'ai fait voir, nous vivons en partie anaerobiquement, des alcaloïdes analogues peuvent et doivent se former dans l'organisme : c'est ce qu'a confirmé l'experience. J'ai donné à ces bases le nom de *leucomaïnes*, qui se borne à indiquer seulement leur origine albuminoïde.

Les produits de la vie aérobie ou anaerobie ne sauraient sans domâge, être longtemps, ou en quantité, retenus dans l'organisme. Regulièrement nous les excretons et les détruisons sans cesse. Mais qu'une émotion frappe les centres nerveux ; qu'un refroidissement arrète le fonctionement de la peau ; que l'air arrive insuffisament au sang ; ou bien que pour une cause plus cachée, les leucomaïnes se produisent plus abondamment dans nos cellules que ces bases soient plus difficilement résorbées, excreteés ou oxydées ; et que des lors le sang s'en charge abondamment et les porte aux centres nerveux qui réglent nos fonctions et président à la vie d'ensemble, aussitot le désordre se généralise, se complete, et suit fatalement sa marche ; en un mot, la maladie apparait et se deroule regulièrement.

Toutefois, il ne faudrait point être trop exclusif, et penser qu'ainsi s'explique, dans tous les cas, la succession des phénomènes morbides. Sans aucun doute beaucoup d'etâts pathologiques résultent des troubles de la nutrition, de l'assimilation, de la desassimilation des sécretions, de l'hématose, &c. . . . et sont, en un mot, de veritables auto-infections. Mais il est des cas où l'on ne saurait méconnaitre l'influence de causes que l'organisme parait impuissant à produire spontanément. On n'a jamais vu la syphilis, la rougeole, la variole, le charbon lui-même . . . ni la plupart des maladies dites contagieuses et spécifiques (à l'exception peut-être du typhus des armées) apparaitre spontanement, même dans les organismes affaiblis, sans contact préalable ou rapport direct ou indirect avec un être préalablement infecté. C'est la gloire de M. Pasteur d'avoir démontré que dans la plupart de ces cas l'on peut retirer de l'organisme malade un microbe specifique cultivable apte à se reproduire au dehors de l'être infecté, et à faire reparaitre la maladie specifique primitive lorsqu'on l'introduit dans un organisme sain. Mais qui ne voit que ces faits trés importants sont un cas particulier de la vie des cellules, telles qu'elles fonctionnent normalement dans les grands animaux ? Le ferment ou microbe specifique vit à la façon d'une des cellules de nos tissus, tantôt *aérobie*, comme lorsqu'il s'agit du charbon ; tantôt *anaerobie*, s'il s'agit par exemple du ferment de la septicémie. Il ne saurait échapper à cette loi qui veut que toute cellule qui vit produise des détritus, des matières extractives, des ptomaïnes et leucomaïnes,

causes prochaines de leur puissante action sur l'organisme. Mais, dans ce nouveau cas, ces cellules étrangères jouissent, à la façon de celles du cancer par exemple, d'une vie, d'une faculté regénératrice intense, et remplissent bientot toute l'organisme des produits dangereux de leur puissante évolution.

Ce serait donc une erreur de dire, avec les élèves trop fervents du Maitre, que toute maladie résulte de l'evolution dans l'organisme d'un microbe spécifique. Il est des causes de maladie qui resident en nous ; elles restent inoffensives tant que se continue l'elimination ou l'oxydation des détritus ; elles eveillent la maladie, si pour une cause quelconque elles s'accumulent dans l'économie et agissent sur les centres nerveux. Mais à ces agents morbigènes dont se débarrassent sans cesse nos tissus vivants, viennent aussi, dans des cas plus rares, se surajouter ceux qui proviennent de la vie normale de ces cellules parasites qu'on a nommées microbes ou ferments, et qu'on rencontre dans la plupart des maladies contagieuses ou virulentes.

Les ptomaïnes et leucomaïnes, comme les matières extractives—l'urèe, les ureides, l'acide carbonique, les oxalates, les sels ammoniacaux—sont donc des résidus de la vie, des matériaux inutiles ou dangereux. Ils peuvent devenir des causes directes de maladie, quelle que soit leur origine, cellules normales de l'organisme ou cellules microbiennes étrangères. De tout ces composés de déchet, les alcaloïdes d'origine animale que la presente publication est destinèe à décrire, sont les plus dignes d'interet. Ils avaient été

inconnus jusqu' à notre époque; et méritent d'autant plus d'être étudiés que leur présence est constante dans nos excretions normales, et qu'ils peuvent être rangés parmi les agents les plus actifs. Aussi je pense que l'excellent livre de M. le Dr. Brown intéressera très particulièrement le public competent, et qu'il contribuera à faire naitre de nouvelles recherches profitables à l'eclaircissement de l'une des questions les plus essentiellement humaines : les causes et le mècanisme de la vie et de la maladie.

ARMAND GAUTIER.

PARIS, le 14 juillet, 1887

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